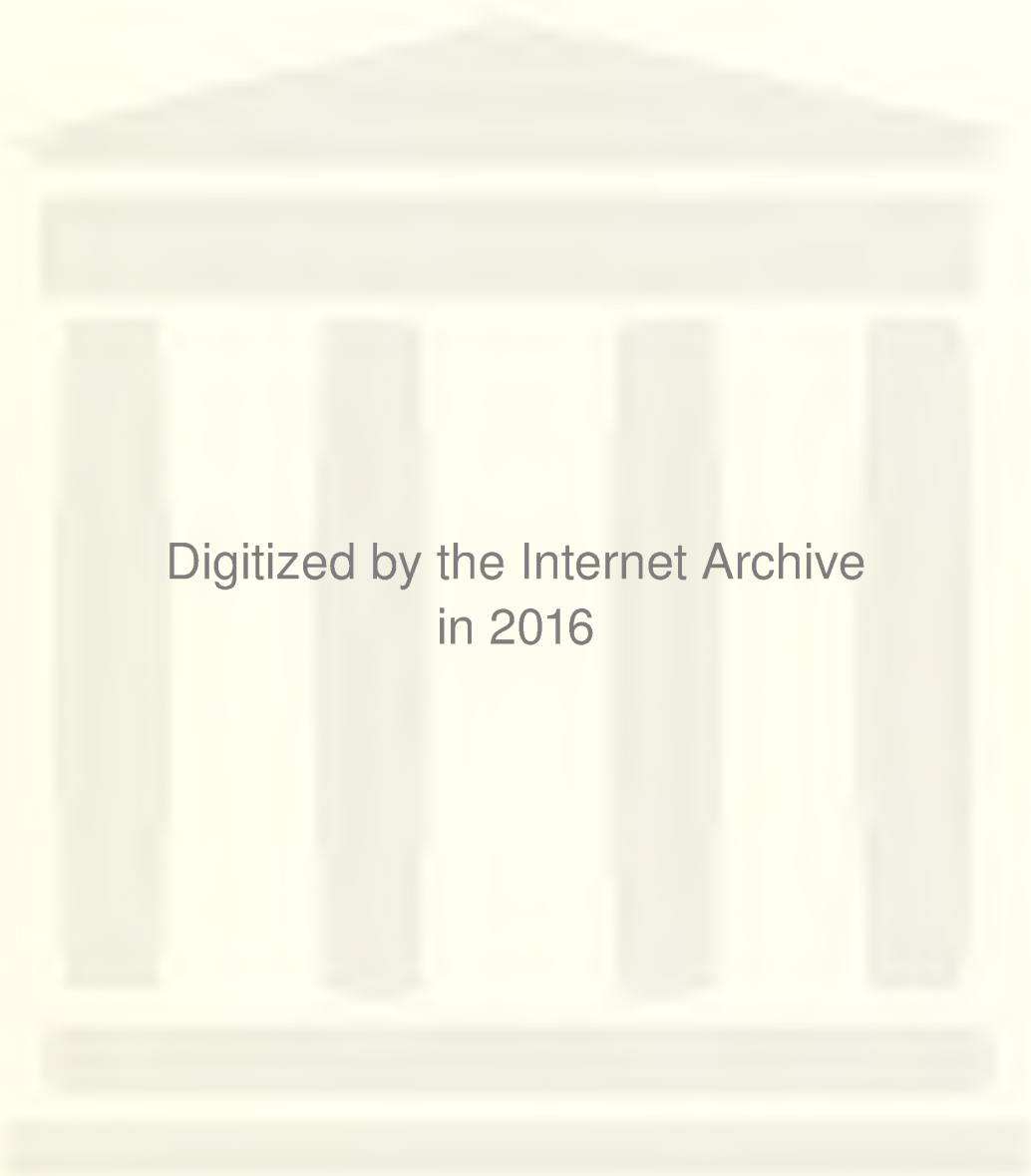
COUNTWAY LIBRARY
HC 3IDZ C

BOSTON MEDICAL LIBRARY
IN THE
FRANCIS A. COUNTWAY
LIBRARY OF MEDICINE


Digitized by the Internet Archive
in 2016

https://archive.org/details/westernjournalof1341cali

THE FRANCIS A. COUNTWAY LIBRARY OF MEDICINE BOSTON JUN 9 1981

THE WESTERN Journal of Medicine

VOLUME 134 • NUMBER 1 **JANUARY 1981**

1 *Myocardial Infarction: A Five-Year Follow-up of Patients*
KARLA K. KISHPAUGH; MARILYN H. FORD, MS; C. HILMON CASTLE, MD, and JAMES C. READING, PhD

7 *Acquired Methemoglobinemia* MITCHELL E. GEFFNER, MD; DARLEEN R. POWARS, MD, and WILLIAM T. CHOCTAW, MD

11 *Bleeding After Liver Biopsy* ANMOL S. MAHAL, MD; C. MICHAEL KNAUER, MD, and PETER B. GREGORY, MD

NUTRITION IN MEDICINE

15 *Hypophosphatemia* JAMES P. KNOCHEL, MD

CLINICOPATHOLOGIC CONFERENCE

27 *Jaundice, Hepatosplenomegaly and Liver Failure in a 60-Year-Old Woman*
Discussants: DAVID J. CAMPISI, MD; CHARLES R. McELROY, MD; J. MICHAEL CRILEY, MD, and FREDRICK GILKEY, MD

MEDICAL STAFF CONFERENCE

34 *The Role of Dietary Fat and Cholesterol in Atherosclerosis and Lipoprotein Metabolism*
Chief Discussant: ROBERT W. MAHLEY, MD, PhD

IMPORTANT ADVANCES IN CLINICAL MEDICINE

43 *Dermatology—Epitomes of Progress*

EDITORIALS

54 • *Deregulation and Governance in Health Care* • *Prognosis After Myocardial Infarction*
• *It's Not Just How Low You Make It, but How You Make It Low*
• *Physicians' Fees—Not Too Bad a Record*

CASE REPORTS

60 *Bicarbonate Therapy for Dysrhythmia and Hypotension in Tricyclic Antidepressant Overdose*
JEROME R. HOFFMAN, MD, and CHARLES R. McELROY, MD

65 *Diabetes Mellitus and Orthostatic Hypotension Resulting From Ingestion of Vacor Rat Poison: Endocrine and Autonomic Function Studies*
KENNETH S. PETERS, MD; THEODORE G. TONG, PharmD; KATHLEEN KUTZ, PharmD, and NEAL L. BENOWITZ, MD

69 *Obstructive Sleep Apnea Syndrome Associated With Nasopharyngeal Carcinoma*
CAPT FRANK M. MOSES, MC, USA, and LT COL JON H. BUSCEMI, MC, USA

CORRESPONDENCE

71 • *Pericardial Effusion in Association With Giant Cell Arteritis* • *Magnesium—It's About Time*
• *Mrs. Laennec and the Stethoscope* • *Protection Against Loss of Bone and Fracture in Postmenopausal Women; With Reply by Author*

SPECIAL ARTICLE

77 *Obstetrics and Gynecology: Considerations in Career Selection* EDMUND STEPHEN PETRILLI, MD

HEALTH CARE DELIVERY

80 *Medical and Health Care in State Residential Institutions for Children—A Report of Survey Findings in Five Hospitals*
A Report of the Committee on Children With Handicaps, Northern California Chapter, American Academy of Pediatrics: ALBERT C. FREMONT, MD, MPH, Chairman; HELEN M. WALLACE, MD, MPH, Subcommittee Chairman; LUCY CRAIN, MD, MPH; KRIST A. BIAKANJA, MD, and NANCY ROIZEN, MD

INFORMATION

87 *Neurosyphilis: An Update* ROGER P. SIMON, MD

92 *Book Reviews* • *Books Received, See Advertising Page 36*

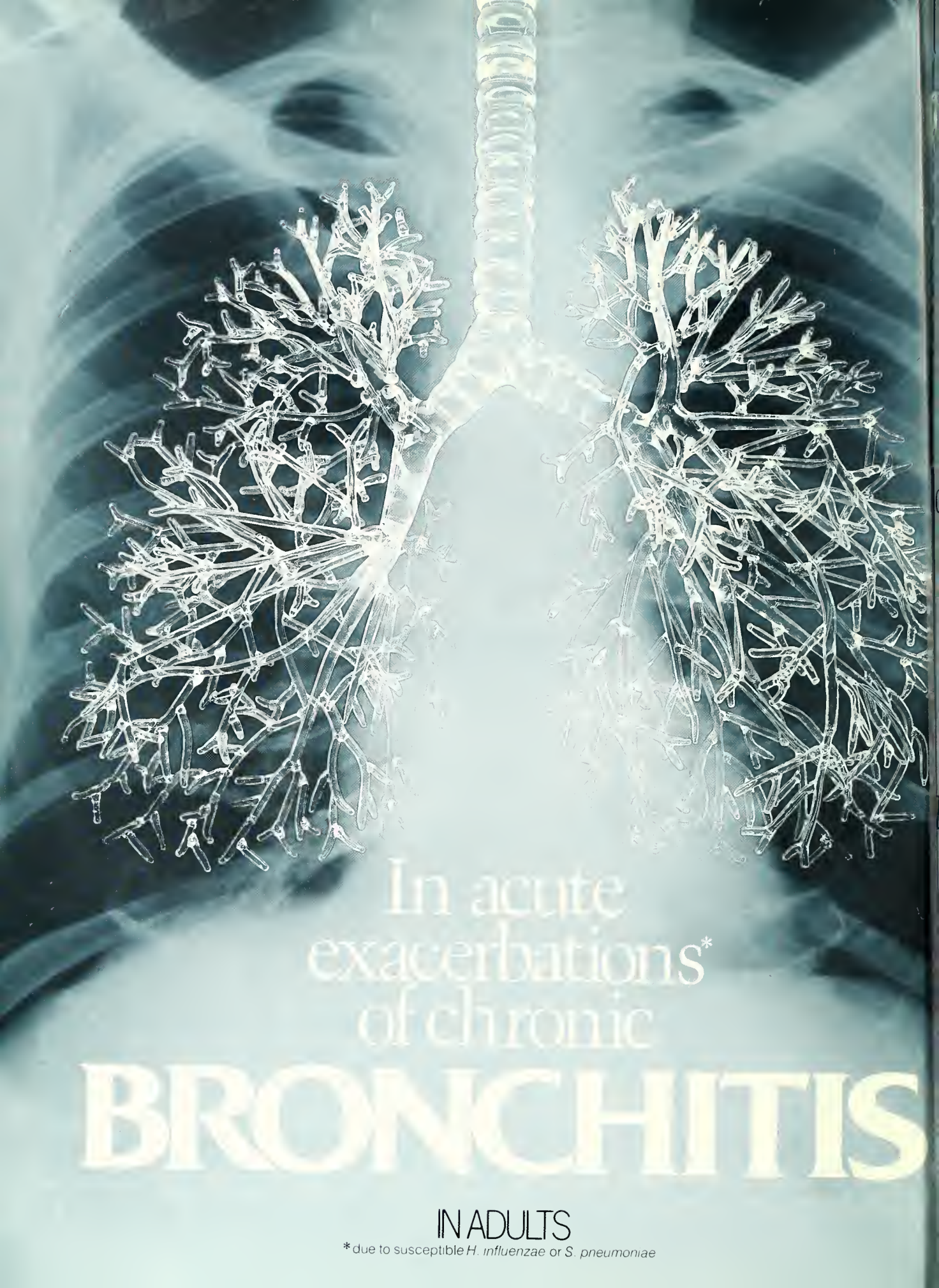
96 *In Memoriam*

Detailed Table of Contents, See Advertising Pages 7 and 8

Information for Authors, See Advertising Page 10

★ **CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA, HAWAII AND NEVADA; ALASKA, MONTANA AND IDAHO; OREGON; WASHINGTON; UTAH**
(See Advertising Page 21)

★★ **Official Journal of the California Medical Association, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association and the Washington State Medical Association**


In acute
exacerbations*
of chronic
BRONCHITIS
IN ADULTS
*due to susceptible H. influenzae or S. pneumoniae

91% overall success rate 7 days posttherapy in controlled multicenter studies involving *H. influenzae* & *S. pneumoniae*†

ROCHE

85%
Causative organism eliminated at end of 14-day treatment (51 of 60 patients)

91%
Causative organism eliminated at 7-day follow-up (50 of 55 patients; 5 patients did not return for follow-up)

- ☐ Low incidence of diarrhea and bronchial superinfection.
- ☐ Gastrointestinal and dermatological reactions were the most frequent side effects in the study.
- ☐ May be used in patients allergic to penicillins and cephalosporins.
- ☐ Convenient b.i.d. dosage encourages compliance.
- ☐ During therapy, maintain adequate fluid intake. Use cautiously in patients with impaired renal or hepatic function, severe allergy or bronchial asthma.

Bactrim is indicated in acute exacerbations of chronic bronchitis in adults when in the physician's judgment it offers an advantage over a single antimicrobial agent.

†Data on file, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

BACTRIM™ DS

Each tablet contains 160 mg trimethoprim and 800 mg sulfamethoxazole.

Please see next page for summary of product information.

BACTRIM™

(trimethoprim and sulfamethoxazole)

ROCHE

A MAJOR ANTIMICROBIAL WITH MULTI-SYSTEM USEFULNESS

The clinical usefulness of Bactrim continues to grow. Now Bactrim is useful for all of the following infections when due to susceptible strains of indicated organisms (see indications section in summary of product information):

UPPER RESPIRATORY

acute otitis media in children

LOWER RESPIRATORY

acute exacerbations of chronic bronchitis in adults —documented *Pneumocystis carinii* pneumonitis

GENITO-URINARY

recurrent urinary tract infections

GASTRO-INTESTINAL

shigellosis

Before prescribing, please consult complete product informa summary of which follows:

Indications and Usage: For the treatment of urinary tract inf to susceptible strains of the following organisms: *Escherichi Klebsiella-Enterobacter, Proteus mirabilis, Proteus vulgaris, Pr gonii.* It is recommended that initial episodes of uncomplicat tract infections be treated with a single effective antibacteria rather than the combination. *Note:* The increasing frequency of re organisms limits the usefulness of all antibacterials, especially in these tract infections.

For acute otitis media in children due to susceptible strains o *Hoemophilus influenzoe* or *Streptococcus pneumoniae* when in cian's judgment it offers an advantage over other antimicrobi clinical information presently available on effectiveness of tr otitis media with Bactrim when infection is due to ampicillin-r *Hoemophilus influenzoe.* To date, there are limited data on the repeated use of Bactrim in children under two years of age. B not indicated for prophylactic or prolonged administration in at any age.

For acute exacerbations of chronic bronchitis in adults due to ble strains of *Haemophilus influenzae* or *Streptococcus pneum* when in physician's judgment it offers an advantage over a sin timicrobial agent.

For enteritis due to susceptible strains of *Shigella flexneri* and *sonnei* when antibacterial therapy is indicated.

Also for the treatment of documented *Pneumocystis carinii* pn To date, this drug has been tested only in patients 9 months to of age who were immunosuppressed by cancer therapy.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides; nursing mothers; infants less than two months of age.

Warnings: BACTRIM SHOULD NOT BE USED TO TREAT STREPT PHARYNGITIS. Clinical studies show that patients with group A β-hemo tococcal tonsillopharyngitis have higher incidence of bacteriologic failure treated with Bactrim than do those treated with penicillin. Deaths from hy sitivity reactions, agranulocytosis, aplastic anemia and other blood dyscra been associated with sulfonamides. Experience with trimethoprim is muc limited but occasional interference with hematopoiesis has been reporte an increased incidence of thrombopenia with purpura in elderly patients o diuretics, primarily thiazides. Sore throat, fever, pallor, purpura or jaundi early signs of serious blood disorders. Frequent CBC's are recommended. should be discontinued if a significantly reduced count of any f blood element is noted.

Precautions: Use cautiously in patients with impaired renal o function, possible folate deficiency, severe allergy or bronchial patients with glucose-6-phosphate dehydrogenase deficiency, h frequently dose-related, may occur. During therapy, maintain ac fluid intake and perform frequent urinalyses, with careful micr examination, and renal function tests, particularly where there paired renal function. Bactrim may prolong prothrombin time in receiving warfarin; reassess coagulation time when administerin to these patients.

Adverse Reactions: All major reactions to sulfonamides and t prim are included, even if not reported with Bactrim. *Blood dysc* Agranulocytosis, aplastic anemia, megaloblastic anemia, thromb leukopenia, hemolytic anemia, purpura, hypoprothrombinemia a methemoglobinemia. *Allergic reactions:* Erythema multiforme, St Johnson syndrome, generalized skin eruptions, epidermal necro ticaria, serum sickness, pruritus, exfoliative dermatitis, anaphyl reactions, periorbital edema, conjunctival and scleral injection, p sensitization, arthralgia and allergic myocarditis. *Gastrointestinal reactions:* stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancre *CNS reactions:* Headache, peripheral neuritis, mental depression, convulsio ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle we and nervousness. *Miscelloneous reactions:* Drug fever, chills, toxic nephrosi oliguria and anuria, periarteritis nodosa and L.E. phenomenon. Due to certa chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides oral hypoglycemic agents, sulfonamides have caused rare instances of goiter tion, diuresis and hypoglycemia in patients; cross-sensitivity with these agent exist. In rats, long-term therapy with sulfonamides has produced thyroid mali

Dosage: Not recommended for infants less than two months of ag

URINARY TRACT INFECTIONS AND SHIGELLOSIS IN ADULTS AND CHILDREN, A

ACUTE OTITIS MEDIA IN CHILDREN:

Adults: Usual adult dosage for urinary tract infections—1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 10-14 days. identical daily dosage for 5 days for shigellosis.

Children: Recommended dosage for children with urinary tract infections or a otitis media—8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 h in two divided doses for 10 days. Use identical daily dosage for 5 days for shige

For patients with renal impairment: Use recommended dosage regimen when creatinine clearance is above 30 ml/min. If creatinine clearance is between 15 ml/min, use one-half the usual regimen. Bactrim is not recommended if crea clearance is below 15 ml/min.

ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS IN ADULTS:

Usual adult dosage: 1 DS tablet (double strength), 2 tablets (single strength) o 4 teasp. (20 ml) b.i.d. for 14 days.

PNEUMOCYSTIS CARINII PNEUMONITIS:

Recommended dosage: 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazol 24 hours in equal doses every 6 hours for 14 days. See complete product inform for suggested children's dosage table.

Supplied: *Double Strength (DS) tablets,* each containing 160 mg trimethoprim a 800 mg sulfamethoxazole, bottles of 100; Tel-E-Dose® packages of 100; Prescript Paks of 20 and 28. *Tablets,* each containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 100 and 500; Tel-E-Dose® packages of 100; Presc Paks of 40. *Pediatric Suspension,* containing in each teaspoonful (5 ml) the equi of 40 mg trimethoprim and 200 mg sulfamethoxazole; cherry flavored—bottles o 16 oz (1 pint). *Suspension,* containing in each teaspoonful (5 ml) the equivalent o 40 mg trimethoprim and 200 mg sulfamethoxazole, fruit-licorice flavored—bottle 16 oz (1 pint).

ROCHE

ROCHE LABORATORIES
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

In Hypertension*...When You Need to Conserve K^+

Every Step of the Way

Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

†Step 1 usually consists of an initial phase (a diuretic alone), a titration phase (dosage adjustment and/or addition of a K^+ supplement or K^+-sparing agent and a maintenance phase (a diuretic alone or in combination with a K^+ supplement or K^+-sparing agent).

Serum K^+ and BUN should be checked periodically (see Warnings).

Before prescribing, see complete prescribing information in SK&F Co. literature or *PDR*. A brief summary follows:

WARNING
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K^+ frequently; both can cause K^+ retention and elevated serum K^+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in postsympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia, although uncommon, has been reported. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components.

Supplied: Bottles of 1000 capsules, Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

©SK&F Co., 1980

SK&F CO.
a SmithKline company
Carolina, P.R. 00630

THE WESTERN Journal of Medicine

Since 1902 (ISSN 0093-0415)

731 MARKET ST. • SAN FRANCISCO, CA 94103 • TELEPHONE (415) 777-2000

Official Journal of the California Medical Association, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association and the Washington State Medical Association

MALCOLM S. M. WATTS, MD, *Editor*
LLOYD H. SMITH, JR., MD, *Associate Editor*
DAVID GREER, *Managing Editor*
BARBARA T. ROONEY, *Assistant Managing Editor*

editorial communications to:
MALCOLM S. M. WATTS, MD, *Editor*

business communications to:
DAVID GREER, *Managing Editor*

MARY KAY COWANS
Advertising Production Manager

Editorial Board

Chairman of the Board
Malcolm S. M. Watts, San Francisco, Ca

Special Editor for Idaho
E. R. W. Fox, Cocur d'Alene, Id

Special Editor for Nevada
Thomas J. Scully, Reno, Nv

Special Editor for Utah
John H. Holbrook, Salt Lake City, Ut

Special Editor for Washington
David Hopkins, Federal Way, Wa

Allergy
Harold S. Novey, Orange, Ca
Abba I. Terr, San Francisco, Ca

Anesthesiology
Ronald L. Katz, Los Angeles, Ca

Cardiac and Thoracic Surgery
John E. Connolly, Irvine, Ca
Albert Starr, Portland, Or

Chest Diseases
Roger K. Larson, Fresno, Ca
Thomas L. Petty, Denver, Co

Dermatology
John H. Epstein, San Francisco, Ca
George F. Odland, Seattle, Wa
Richard B. Stoughton, San Diego, Ca

General and Family Practice
Daniel D. Roberts, Central Point, Or
Harmon E. Holverson, Emmett, Id
Wilfred Snodgrass, Santa Monica, Ca

General Surgery
Fred M. Anderson, Reno, Nv
Daniel T. Cloud, Phoenix, Az
Paul A. Ebert, San Francisco, Ca
Lucius D. Hill, Seattle, Wa
Frank G. Moody, Salt Lake City, Ut

Industrial Medicine and Toxicology
Thomas H. Milby, Berkeley, Ca

Internal Medicine
Robert W. Burrough, Spokane, Wa
Theodore C. Eickhoff, Denver Co
Robert L. Hare, Portland, Or
Robert H. Moser, Philadelphia, Pa
George A. Porter, Portland, Or
Helen M. Ranney, San Diego, Ca
David D. Ulmer, Los Angeles, Ca
Edgar Wayburn, San Francisco, Ca
Ralph C. Williams, Jr., Albuquerque, NM

Neurology
Pierre M. Dreyfus, Sacramento, Ca
Philip D. Swanson, Seattle, Wa
W. C. Wiederholt, La Jolla, Ca

Neurosurgery
John R. Green, Phoenix, Az
Arthur A. Ward, Jr., Seattle, Wa
Charles B. Wilson, San Francisco, Ca

Nuclear Medicine
Joseph P. Kriss, Stanford, Ca

Obstetrics and Gynecology
Ralph C. Benson, Portland, Or
Ralph W. Hale, Honolulu, Hi
W. LeRoy Heinrichs, Stanford, Ca
Morton A. Stenchever, Seattle, Wa

Ophthalmology
Robert S. Hepler, Los Angeles, Ca
Bruce E. Spivey, San Francisco, Ca

Orthopedics
Ernest M. Burgess, Seattle, Wa
Duane M. Kline, Jr., Cheyene, Wy

Otolaryngology
Roger Boles, San Francisco, Ca
Mansfield F. W. Smith, San Jose, Ca

Pathology
Richard L. Kempson, Stanford, Ca

Pediatrics
Louis K. Diamond, San Francisco, Ca
William L. Nyhan, San Diego, Ca
Irving Schulman, Stanford, Ca
Arnold L. Smith, Seattle, Wa

Pharmacology
George N. Aagaard, Seattle, Wa

Physical Medicine and Rehabilitation
Glenn G. Reynolds, San Jose, Ca

Plastic Surgery
Richard P. Jobe, Los Altos, Ca
N. John Wilde, Fresno, Ca

Psychiatry
Carl Eisdorfer, Seattle, Wa
Alan I. Levenson, Tucson, Az
Helen Tausend, Beverly Hills, Ca
Joe Paul Tupin, Sacramento, Ca

Public Health
J. M. Stubblebine, Greenbrae, Ca
Irma M. West, Sacramento, Ca

Radiology
M. Paul Capp, Tucson, Az
Melvin M. Figley, Seattle, Wa
Marshall Rowen, Orange, Ca

Urology
Richard Middleton, Salt Lake City Ut
Thomas A. Stamey, Stanford Ca

Consulting Editor
Medical Services and Health Care
Paul J. Sanazaro, Berkeley, Ca

Policy Committee—Editorial Board

JOSEPH F. BOYLE ..... Los Angeles
BRAD COHN ..... San Francisco
GLADDEN V. ELLIOTT ..... La Mesa
SAMUEL HOROWITZ ..... Los Angeles
ROBERT D. BURNETT ..... Sunnyvale
THEODORE W. LORING ..... Eureka
MALCOLM S. M. WATTS ..... San Francisco

Advertisements—THE WESTERN JOURNAL OF MEDICINE is published the first week of each month. Advertising copy must be received not later than the first of the month preceding issue. Advertising rates will be sent on request. Acceptance of advertising is contingent upon approval by the Advertising Committee. The journal reserves the right to reject any advertisement.

ADVERTISING SALES REPRESENTATIVES:

EAST:
SAUL HORNIK
P.O. BOX 246
MORGANVILLE, NJ 07751
TEL: (201) 591-9234

MIDWEST:
R. C. JOHNSON & ASSOCIATES
RICHARD C. JOHNSON
547 WEST MELROSE
CHICAGO, IL 60657
TEL: (312) 327-6969

WEST:
MEDIA SERVICES
DARIEN DELORENZO
LYNNE JEFFES
2612 BELMONT CANYON RD.
BELMONT, CA 94002
TEL. (415) 595-2203
(415) 348-7478

CLASSIFIED:
731 MARKET ST.
SAN FRANCISCO, CA 94103
TEL. (415) 777-2000
(415) 777-0424

Copyright 1980 by the California Medical Association
Owned and Published by the California Medical Association
All material subject to this copyright appearing in THE WESTERN JOURNAL OF MEDICINE may be photocopied for the noncommercial purpose of scientific or educational advancement. Volumes begin with the first of January and the first of July.

The subscription price per year is $10 in the United States and Canada; $18 in all other countries. Single copies are $2. Address all subscription communications to THE WESTERN JOURNAL OF MEDICINE Circulation, 731 Market St., San Francisco, CA 94103.

Allow six weeks for subscriptions to begin. Past issues must be bought individually. So long as reserve stocks are available, missing issue requests from subscribers are honored for up to six months after the issue date. Thereafter, the single copy rate of $2.00 is applicable for each issue available.

"Change of Address"—Requests for change of address should give both the old and new addresses. Allow six weeks for change-over.

CONTRIBUTIONS OF SCIENTIFIC AND ORIGINAL ARTICLES

Responsibilities for Statements and Conclusions in Original Articles—Authors are responsible for all statements, conclusions and methods of presenting their subjects. These may or may not be in harmony with the views of the editorial staff. It is aimed to permit authors to have as wide latitude as the general policy of the journal and the demands on its space may permit. The right to reduce, revise or reject any manuscript is always reserved.

Exclusive Publication—Articles are accepted for publication on condition that they are contributed solely to this journal. Ordinarily contributors will be notified within 60 days if a manuscript is accepted for publication. Every effort will be made to return unused manuscripts.

Length of Articles—Ordinarily articles should not exceed 3,000 words (approximately five printed pages). Under exceptional circumstances only will articles of over 4,000 words be published.

Manuscripts—Manuscripts should be typewritten and double-spaced, and the *original* typescript plus two copies should be submitted.

Illustrations—Ordinarily publication of two or three illustrations accompanying an article will be paid for by THE WESTERN JOURNAL OF MEDICINE. Any number beyond this may have to be paid for by the author.

References—References should conform to the following order: name of author, title of article, name of periodical, and volume with inclusive pages, month and year—i.e., Lee GS: The heart rhythm following therapy with digitalis—In theory and practice. Arch Int Med 44:554-562, Dec 1942. They should be listed in the order in which they are cited in the text, numbered in sequence and punctuated as above.

Reprints—Reprints must be paid for by the author at established standard rates.

"Information for Authors" Available on request or see January 1981 issue, advertising page 10.

"Entered as second class matter at the post office in San Francisco under the Act of March 3, 1879." Acceptable for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized August 10, 1918. Publication Number 084480.

His Master's Choice

You make important decisions as a matter of routine. As the manager of a complex business you now have some exciting choices in the area of information management.

Brig Computers & Software has developed the most sophisticated medical office management program for the efficient handling of billing, accounts receivable, claim forms, and patient data filing.

And that's just the beginning. When you decide to equip your office with Brig Computers & Software you will do more than simply automate your billing.

Your present office staff will now provide you with daily, month-to-date, and year-to-date reports, with charges arranged by diagnosis, by transaction, and by physician.

For less than the cost of an outside billing service you can have a complete system installed. Call today for a personal demonstration.

BRIG

COMPUTERS & SOFTWARE

5830 Uplander Way, Culver City, CA 90230

(213) 641-3297 TWX 910-328-6162 in CA 1 (800) 772-2666 ext. 904 in USA 1 (800) 227-2400 ext. 904

includes Alaska, Hawaii, Puerto Rico and the Virgin Islands

Acute pain is no laughing matter.

The first prescription for the first days of acute pai

Empirin® c̄ Codeine #3

Each tablet contains: aspirin, 325 mg; plus codeine phosphate, 30 mg, (Warning — may be habit-forming). Ⓒ III

For the millions of patients who need the potency of aspirin and codeine for their acute pain.

The pain of fractures, strains, sprains, burns and wounds is at its peak during the first three to four days following trauma. The potent action of Empirin c̄ Codeine begins to work within 15 minutes of oral administration, an important advantage during this acute pain period. Empirin c̄ Codeine has unique bi-level action to attack pain at two critical points: peripherally at the site of injury and centrally at the site of pain awareness.

For the most effective dosage in treating acute pain, begin with... two tablets of Empirin c̄ Codeine #2 or #3, every four hours. Titrate downward as pain subsides.

EMPIRIN® with Codeine

Ⓒ III

DESCRIPTION: Each tablet contains aspirin (acetylsalicylic acid) 325 mg plus codeine phosphate in one of the following strengths: No. 2 — 15 mg, No. 3 — 30 mg, and No. 4 — 60 mg (Warning — may be habit-forming.)

CONTRAINDICATIONS: Hypersensitivity to aspirin or codeine

WARNINGS:

Drug dependence: Empirin with Codeine can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of this drug and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral, narcotic-containing medications. Like other narcotic-containing medications, the drug is subject to the Federal Controlled Substances Act.

Use in ambulatory patients: Empirin with Codeine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using this drug should be cautioned accordingly.

Interaction with other central nervous system (CNS) depressants: Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics, or other CNS depressants (including alcohol) concomitantly with Empirin with Codeine may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Use in pregnancy: Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, Empirin with Codeine should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

PRECAUTIONS:

Head injury and increased intracranial pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions: The administration of Empirin with Codeine or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Allergic: Precautions should be taken in administering salicylates to persons with known allergies. Patients with nasal polyps are more likely to be hypersensitive to aspirin.

Special risk patients: Empirin with Codeine should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture, peptic ulcer, or coagulation disorders.

ADVERSE REACTIONS: The most frequently observed adverse reactions to codeine include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients and some of these adverse reactions may be alleviated if the patient lies down. Other adverse reactions include euphoria, dysphoria, constipation, and pruritus.

The most frequently observed reactions to aspirin include headache, vertigo, ringing in the ears, mental confusion, drowsiness, sweating, thirst, nausea, and vomiting. Occasional patients experience gastric irritation and bleeding with aspirin. Some patients are unable to take salicylates without developing nausea and vomiting. Hypersensitivity may be manifested by a skin rash or even an anaphylactic reaction. With these exceptions, most of the side effects occur after repeated administration of large doses.

DOSAGE AND ADMINISTRATION: Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. Empirin with Codeine is given orally. The usual adult dose for Empirin with Codeine No. 2 and No. 3 is one or two tablets every four hours as required. The usual adult dose for Empirin with Codeine No. 4 is one tablet every four hours as required.

DRUG INTERACTIONS: The CNS depressant effects of Empirin with Codeine may be additive with that of other CNS depressants. See WARNINGS.

Wellcome

Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

THE WESTERN

Journal of Medicine

VOLUME 134 • NUMBER 1 **JANUARY 1981**

TABLE OF CONTENTS

1 *Myocardial Infarction: A Five-Year Follow-up of Patients*
KARLA K. KISHPAUGH; MARILYN H. FORD, MS; C. HILMON CASTLE, MD, and JAMES C. READING, PhD
From the Department of Family and Community Medicine, University of Utah College of Medicine, Salt Lake City.

7 *Acquired Methemoglobinemia* MITCHELL E. GEFFNER, MD; DARLEEN R. POWARS, MD, and WILLIAM T. CHOCTAW, MD
From the Department of Pediatrics and the Burn Center, Department of Surgery, University of Southern California School of Medicine, Los Angeles.

11 *Bleeding After Liver Biopsy* ANMOL S. MAHAL, MD; C. MICHAEL KNAUER, MD, and PETER B. GREGORY, MD
From the Department of Medicine, Stanford University School of Medicine, Stanford, California; Santa Clara Valley Medical Center, San Jose, California, and Veterans Administration Medical Center, Palo Alto, California.

NUTRITION IN MEDICINE

15 *Hypophosphatemia* JAMES P. KNOCHEL, MD
From the Medical Service, Veterans Administration Medical Center, Dallas, and the Department of Internal Medicine, University of Texas Southwestern Medical School, Dallas.

CLINICOPATHOLOGIC CONFERENCE

27 *Jaundice, Hepatosplenomegaly and Liver Failure in a 60-Year-Old Woman*
Discussants: DAVID J. CAMPISI, MD; CHARLES R. McELROY, MD; J. MICHAEL CRILEY, MD, and FREDRICK GILKEY, MD
From the Department of Medicine, UCLA School of Medicine, Center for the Health Sciences, Los Angeles.
An edited transcript of a Clinical Pathologic Conference held in 1980 at the UCLA Center for the Health Sciences, Los Angeles. This transcript was edited by David J. Campisi, MD, and John L. Sherman, MD.

MEDICAL STAFF CONFERENCE

34 *The Role of Dietary Fat and Cholesterol in Atherosclerosis and Lipoprotein Metabolism*
Chief Discussant: ROBERT W. MAHLEY, MD, PhD
A discussion selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from a transcription, it was prepared by Drs. David W. Martin, Jr, Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine.

IMPORTANT ADVANCES IN CLINICAL MEDICINE

Dermatology—Epitomes of Progress
Items of progress in dermatology. Each item in the judgment of a panel of knowledgeable physicians has recently become reasonably firmly established, both as to scientific fact and important clinical significance.

43 *High Doses of Aspirin in the Treatment of Mucocutaneous Lymph Node Syndrome*
ALVIN H. JACOBS, MD

44 *Acral Lentiginous Melanoma* DAVID R. TAYLOR, Jr, MD

44 *Newer Aspects of the Use of Anthralin in Psoriasis*
LEONARD H. GOLDBERG, MD, and MARGARET STEWART, MD

45 *Lymphomatoid Papulosis* DAVID G. DENEAU, MD

46 *Inflammatory Lesions of Acne Vulgaris: Current Concepts* JUD R. SCHOLTZ, MD

47 *Update on the Use of Retinoids* DANIEL A. PARDINI, MD

48 *New Developments in the Staging and Therapy of Mycosis Fungoides*
NORMAN M. PRICE, MB, ChB

49 *Skin Lesions in Bowel Bypass Syndrome* FOY W. COX, MD

50 *PUVA Carcinogenesis* ELIZABETH A. ABEL, MD

51 *ANA-Negative Systemic Lupus Erythematosus* DOROTHY J. BUCKNER, MD

51 *New Pustular Dermatoses of Infants* DAVID A. SOUTH, MD

52 *Practical Advances in Immunohistology* JAMES H. BECKETT, MD

EDITORIALS

54 *Deregulation and Governance in Health Care*

55 *Prognosis After Myocardial Infarction* STEPHEN C. ACHUFF, MD
From the Department of Medicine, The Johns Hopkins University School of Medicine, Baltimore.

(Continued on Next Page)

56 *It's Not Just How Low You Make It, but How You Make It Low* R. CURTIS MORRIS, Jr, MD
From the General Research Center, University of California, San Francisco.

59 *Physicians' Fees—Not Too Bad a Record*

CASE REPORTS

60 *Bicarbonate Therapy for Dysrhythmia and Hypotension in Tricyclic Antidepressant Overdose*
JEROME R. HOFFMAN, MD, and CHARLES R. McELROY, MD
From the Department of Medicine, Division of Emergency Medicine, UCLA, Center for the Health Sciences, Los Angeles.

65 *Diabetes Mellitus and Orthostatic Hypotension Resulting From Ingestion of Vacor Rat Poison: Endocrine and Autonomic Function Studies*
KENNETH S. PETERS, MD; THEODORE G. TONG, PharmD; KATHLEEN KUTZ, PharmD, and NEAL L. BENOWITZ, MD
From the Clinical Pharmacology Unit of the Medical Service, San Francisco General Hospital Medical Center, and the Departments of Medicine and Clinical Pharmacy, University of California, San Francisco.

69 *Obstructive Sleep Apnea Syndrome Associated With Nasopharyngeal Carcinoma*
CAPT FRANK M. MOSES, MC, USA, and LT COL JON H. BUSCEMI, MC, USA
From the Department of Medicine and Neurology Service, Department of Medicine, Fitzsimons Army Medical Center, Aurora, Colorado.

CORRESPONDENCE

71 *Pericardial Effusion in Association With Giant Cell Arteritis*
HARINDER S. GAREWAL, MD, PhD; RICHARD F. UHLMANN, MD, and ROBERT M. BENNETT, MD

72 *Magnesium—It's About Time* BERNARD HORN, MD

73 *Mrs. Laennec and the Stethoscope* E. R. W. FOX, MD

Protection Against Loss of Bone and Fracture in Postmenopausal Women

74 ROBERT P. HEANEY, MD

75 ELMER E. SPECHT, MD, Replies

SPECIAL ARTICLE

77 *Obstetrics and Gynecology: Considerations in Career Selection* EDMUND STEPHEN PETRILLI, MD
From the Department of Obstetrics and Gynecology, UCLA Center for the Health Sciences, Los Angeles.

HEALTH CARE DELIVERY

80 *Medical and Health Care in State Residential Institutions for Children and Youths—A Report of Survey Findings in Five Hospitals*
A Report of the Committee on Children With Handicaps, Northern California Chepter, American Academy of Pediatrics: ALBERT C. FREMONT, MD, MPH, Chairman; HELEN M. WALLACE, MD, MPH, Subcommittee Chairman; LUCY CRAIN, MD, MPH; KRIST A. BIAKANJA, MD, and NANCY ROIZEN, MD

INFORMATION

87 *Neurosyphilis: An Update* ROGER P. SIMON, MD
From the Department of Neurology, San Francisco General Hospital, and University of California, San Francisco.

BOOK REVIEWS

92 *MGH Textbook of Emergency Medicine—Emergency Care as Practiced at the Massachusetts General Hospital*
by EARLE W. WILKINS, Jr, MD; JAMES J. DINEEN, MD, and ASHBY C. MONCURE, MD, Editors
Reviewed by JOHN E. CONTE, Jr, MD, and WILLIAM F. OWEN, Jr, MD

92 *Repiratory Function of the Lung and Its Control*
by FRED S. GRODINS, MD, PhD, and STANLEY M. YAMASHIRO, PhD
Reviewed by GIBBE H. PARSONS, MD

93 *Textbook of Geriatric Medicine and Gerontology—Second Edition*
by J. C. BROCKLEHURST, MD, MSc, FRCP (Glas and Ed), Editor
Reviewed by ALEX COMFORT, MD

93 *Thyroid Cancer* by LARRY D. GREENFIELD, MD, Editor
Reviewed by FRANCIS S. GREENSPAN, MD

94 *The Metabolic Management of the Critically Ill* by DOUGLAS W. WILMORE, MD
Reviewed by GLENN D. BRAUNSTEIN, MD

94 *Antimicrobial Prescribing* by HAROLD C. NEU, MD
Reviewed by JAMES J. PLORDE, MD

94 *Drug Interactions—Clinical Significance of Drug-Drug Interactions and Drug Effects on Clinical Laboratory Results—Fourth Edition*
by PHILIP D. HANSTEN, PharmD
Reviewed by LARRY A. WHEELER, PhD

95 *Computers for the Physician's Office—Volume II in the Medical Computing Series*
by JOAN ZIMMERMAN, D Phil
Reviewed by MARSDEN S. BLOIS, MD, PhD

96 *In Memoriam*

Books Received, See Advertising Page 36

Information for Authors, See Advertising Page 10

★ CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA, HAWAII AND NEVADA, ALASKA MONTANA AND IDAHO; OREGON; WASHINGTON UTAH
(See Advertising Page 21)

★★ Official Journal of the California Medical Association, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association and the Washington State Medical Association

Practice what we teach.

Today there are over 31 million men, women and children suffering from the many forms of arthritis and related rheumatic diseases. And there just aren't enough trained rheumatologists to help them.

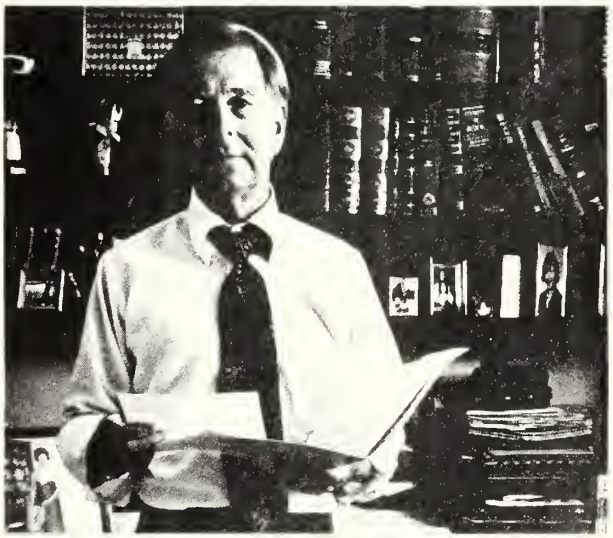
That's why arthritis sufferers need your help.

They must depend heavily on the family practitioner for better diagnosis, more effective patient treatment.

Contact your local Arthritis Foundation chapter for the latest information on arthritis. This includes continuing educational seminars by leading rheumatologists, scientific meetings, "outreach" programs—as well as the "Bulletin on the Rheumatic Diseases," "Arthritis and Rheumatism Journal," "Primer on the Rheumatic Diseases," audio cassettes and other professional materials. Free disease handbooks and medication pamphlets are also available to patients.

Please. Let us help your practice with what we teach.

The Arthritis Foundation helps doctors help.



ARTHRITIS FOUNDATION

INFORMATION FOR AUTHORS

Submitting Manuscripts

Manuscripts for consideration should be sent to the editor, Malcolm S. M. Watts, MD, 731 Market Street, San Francisco, California 94103. The transmittal letter should designate one person as correspondent and include complete address, with ZIP code and telephone number.

In view of *The Copyright Revision Act of 1976,* transmittal letters should contain the following language: "In consideration for reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns or otherwise conveys all copyright ownership to THE WESTERN JOURNAL OF MEDICINE in the event that such work is published by the journal." This statement should be signed by *all* the authors.

Authors are urged to seek clarity and succinctness in all manuscripts regardless of subject matter or format, and to give close attention to syntax, grammar and spelling.

Preparing Manuscripts

The original manuscript and *two* copies should be submitted on heavy bond paper (8½ by 11 inches, *not* erasable), typed double-spaced throughout (including legends, tables and references) on one side of the paper, with 1½-inch margins. Ordinarily, articles should not exceed 2,000 words (less than 15 text pages, typed double-spaced). Under exceptional circumstances only will articles longer than 4,000 words be published. Pages should be numbered consecutively, beginning with the title page.

Style

Abbreviations. Use of abbreviations should be minimized. If they are necessary, abbreviations should be spelled out at first mention, with the abbreviation itself immediately following in parentheses.

Weights and measures. All measurements should be given in metric units. English equivalents should be given parenthetically if the measurements were originally done in English units.

Temperatures. Temperature readings should be given first in Celsius, followed by the Fahrenheit equivalent in parentheses.

Drug names. If the trade name of a drug is used, the generic name should be given first, followed by the trade name in parentheses. Trade names are capitalized, generic names are not.

Title Page

Titles are best when brief and concise. The title page should include the full name of the author(s), with degrees, academic or professional titles, complete addresses and any institutional or other affiliations. The complete name and address of the person who will handle reprint requests also should appear on this page.

Abstract

The abstract (approximately 150 words) should be a short summary, saying in brief what is said at length in the body of the article—rather than such and such "is discussed," "is presented" or "was investigated."

Tables and Figures

Tables

Each table should be typed on a separate sheet of paper, be numbered consecutively in Arabic numerals, have a brief descriptive title and have its position indicated in the text.

Illustrations (Figures)

Three sets of clear, unmounted black and white glossy prints of figures should be submitted (preferably 5 by 7 inches, but no larger than 8½ by 11 inches). For line drawings, original artwork or glossy prints are acceptable. Illustrations should be numbered consecutively in Arabic numerals and their position indicated in the text. Figure number, first author's name and top of the photo should be shown on the reverse side of each illustration. Recognizable photographs of patients are to be masked and written permission for publication obtained from the patients.

Legends

All legends for figures should be typed together on a separate sheet of paper. Magnification and stain for photomicrographs should be indicated in parentheses.

Permission for Reproduction

If an illustration or table has been used previously in another publication, written permission for its use must be obtained from the publisher, and should accompany the manuscript. The source should be acknowledged in the legend if it can be done briefly by citation of a reference number. Otherwise, acknowledgment is made at the end of the figure legend or at the bottom of the table.

References

References should be limited to those cited in the text. They must be typed double-spaced and numbered consecutively as they appear in the manuscript. (See examples below for style.) Abbreviations of journal titles should conform to those used in *Index Medicus.*

Journal Articles

Note handling of multiple authorship. If more than three authors are listed as contributors, use "et al" to designate those names after the first three. Also note capitalization, punctuation, mention of inclusive page numbers, and month and year of publication. Separate the subtitle from the title by either a dash or a colon. Use colon *only* if it appears in the original citation.

1. Jones JS, Anderson HW, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 292:444-456, Apr 26, 1978

2. Graybill JR, Alford RH, Smith RG, et al: Cell-mediated immunity in cryptococcosis: A brief review. Cell Immunol 7: 76-79, Sep 1978

Books

Note handling of "edition," "editor(s)," and "volume," as well as appropriate sequence of reference information and capitalization of chapters and titles.

3. Berne EJ, Smith TL: Role playing in therapy, chap 2, Principles of Group Therapy. New York, Oxford University Press, 1966, pp 35-51 *(author of chapter same as author of book)*

4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, IL, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

Pamphlets, Monographs or Books With No Given Author

5. AMA Department of Drugs: AMA Drug Evaluation, 3rd Ed. Littleton, MA, Publishing Sciences Group, Inc, 1977 *(corporate author)*

6. Compilation of Standard Definitions, 3rd Ed. Philadelphia. American Society for Testing and Materials, 1976 *(no given author; give name and place of publisher)*

Articles in Press or Accepted for Publication

Any article accepted for publication should include the name of the journal (appropriately abbreviated) in which it will appear, and the phrase "in press" or "accepted for publication" in place of the date of publication.

Personal Communications and Unpublished Data

This information should *not* be included in the reference list but should be given in parentheses within the body of the text. Date of communication, whether it was personal or written, and the person's name, highest academic degree and professional affiliation should be provided.

Acknowledgments

It is the policy of the *WJM* not to print acknowledgments, the feeling being that if a person has contributed enough to a paper to be mentioned, he or she should be included among the authors, or the contribution should be mentioned in the body of the paper or in a footnote.

Correspondence

Brief manuscripts commenting on articles that have appeared in the journal, containing information of interest to physicians or discussing issues of the day will be considered for publication. Very short reports of cases, clinical experience, clinical studies, adverse effects and the like also will be considered. Items for the Correspondence section should not exceed 600 words and should have no more than five bibliographic references and one figure or table.

Author Responsibility

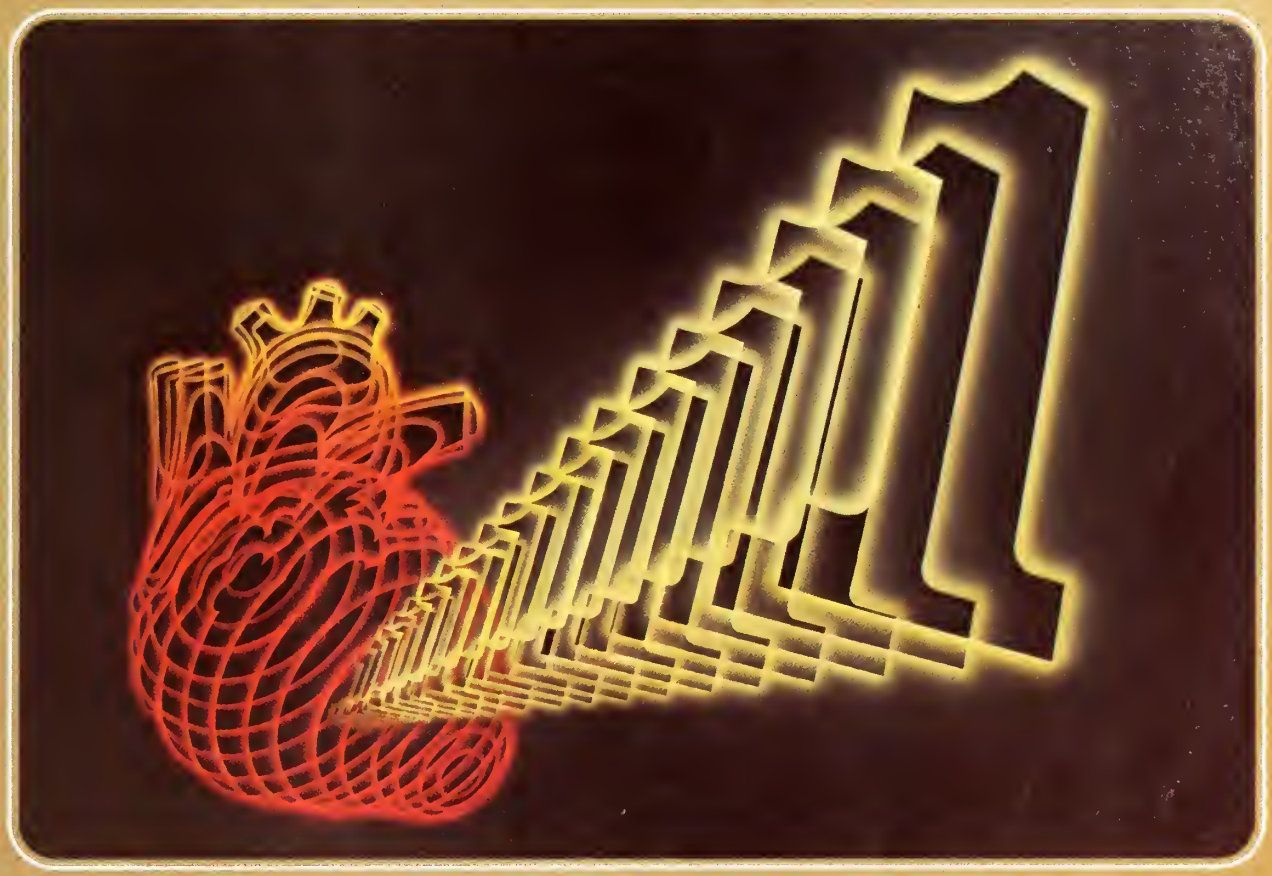
Authors are responsible for all statements made in articles. Manuscripts are considered for publication with the explicit understanding that they are original, have not been published previously and are not simultaneously under consideration by any other publication.

All accepted manuscripts are subject to copy editing, and authors are sent edited galleys for approval. No changes will be made after the final, edited version has been approved by the author.

Reprints

If reprints are desired, they must be paid for by the author. A reprint order form with schedule of prices is sent to the author when the article is published. Authors are responsible for handling requests for reprints of their articles.

CORGARD®
nadolol tablets

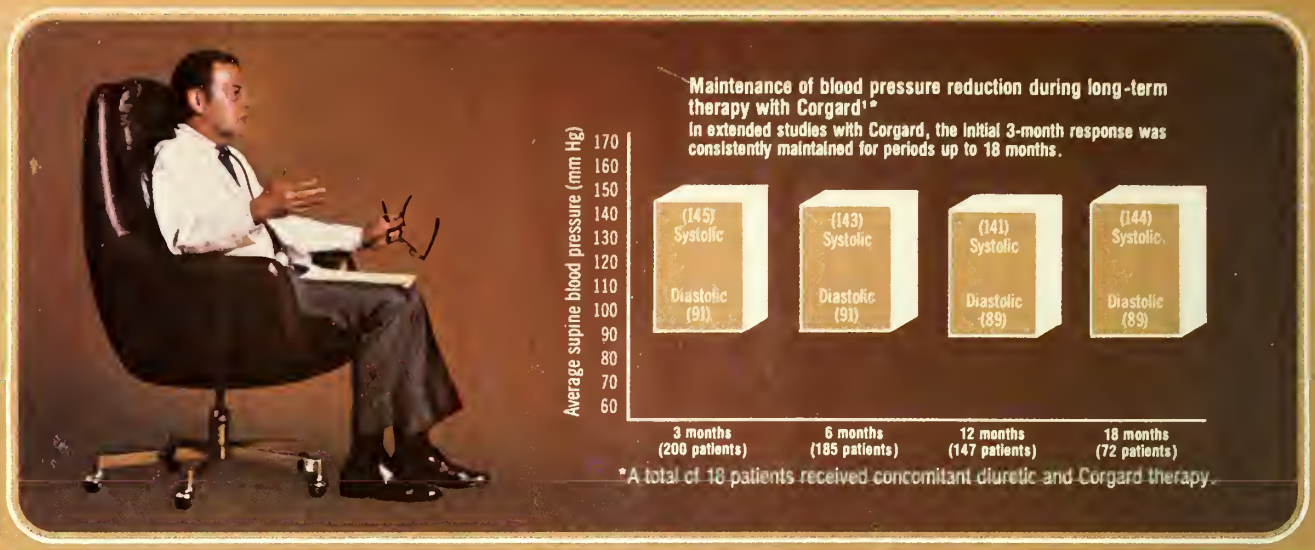


The first beta-blocker with once-a-day dosage

Round-the-clock protection in the control of hypertension

SQUIBB

See last page of this advertisement for brief summary.



When you prescribe...

CORGARD® (nadolol tablets) ...for significant blood pressure reduction

In short-term clinical studies of 114 patients with mild, moderate and severe hypertension, Corgard taken in single daily doses of 40–320 mg (mean: 200 mg) achieved a significant overall reduction in supine and standing blood pressure in 94% of patients — this included 62.3% of the patients who achieved normalized supine diastolic pressure (≤ 90 mm Hg).

...for comparable efficacy, once a day, to propranolol, four times a day

In a controlled clinical comparison of 179 patients with mild, moderate and severe hypertension, Corgard, once a day, was as effective in reducing supine and standing pressure as propranolol, four times a day.[1]

...for extended protection in control of mild, moderate and severe hypertension

Corgard provides round-the-clock control of hypertension by reducing elevated systolic and diastolic blood pressure — with a single daily dose.

They can comply.

CORGARD® (nadolol tablets) ...promotes compliance with a single daily dose

The 20- to 24-hour serum half-life of Corgard offers round-the-clock reduction in blood pressure with a once-daily dosage. With no need to interrupt daily activities to take multiple doses of medication, patients are more likely to comply.

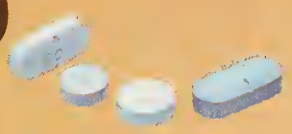
...is often effective alone, without a diuretic[1]

Control of blood pressure with a single agent also simplifies the patient's medication schedule. Only one medication once a day means less likelihood of forgotten or skipped doses.

...rarely causes impotence, loss of libido, orthostatic hypotension*

Because it is virtually free from these undesirable side effects, the patient can function normally, without undue concern.

Prescribe CORGARD® nadolol tablets



40 mg, 80 mg, 120 mg, and 160 mg tablets

The common-sense beta-blocker for hypertension

SQUIBB

*Please see brief summary for discussion of Contraindications, Adverse Reactions, Precautions, and Warnings, including avoidance of abrupt withdrawal, on next page of this advertisement.

100% FINANCING

YES! OWN YOUR
MEDICAL OFFICE BLDG.
WITH 100% FINANCING
WITH THE

HFD
TOTAL SERVICE CONCEPT

HFD

DOES SITE SELECTION, ZONING, LAND PURCHASING, ARCHITECTURAL ENGINEERING, AND ELECTRICAL.

HFD

PROVIDES ECONOMIC FEASIBILITY STUDIES, LEGAL & ACCOUNTING, TENANTS LEASES, RECRUITS ADDITIONAL TENANTS.

HFD

SELECTS BUILDING MATERIALS, CREATES LANDSCAPE DESIGN, EQUIPMENT LEASING, COMPUTER BILLING SERVICES, AND INTERIOR DESIGN.

HFD

PREPARES APPLICATIONS FOR CONSTRUCTION AND PERMANENT LOANS, PROPERTY MANAGEMENT.

PLUS OBTAINS
ALL EQUITY CASH NEEDED
FOR TOTAL TURN-KEY PROJECT
– (ONE GUARANTEED PRICE) –

HFD

TO ANSWER YOUR QUESTIONS
CALL LEN KAPLAN
(714) 481-1274
Health Facilities Development, Inc.
777 So. Pacific Coast Hwy. #206
Solana Beach, CA 92075

YOUR CONCEPT SOUNDS GREAT!
☐ LET'S SET UP A MEETING
☐ HAVE QUESTIONS, CALL US

Dr./Mr./Ms _____

Address _____

Telephone _____

City _____

State _____ Zip _____

Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

Ativan® (IV) for (lorazepam) Anxiety

Dosage: **Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.**

How Supplied: **0.5, 1.0 and 2.0mg tablets.**

Wyeth Laboratories
Philadelphia, PA 19101

Copyright © 1981 Wyeth Laboratories. All rights reserved.

Why one benzodiazepine and not another?

Are you concerned about long-acting metabolites? Many clinicians, as well as pharmacologists, are beginning to draw attention to this problem (see New England Journal of Medicine, April 5, 1979).

In contrast to some older benzodiazepines, Ativan (lorazepam) does not give rise to long-lasting active metabolites. As with all benzodiazepines, you should follow the usual precautions concerning co-administration with other CNS depressants and warn your patients against operating dangerous machinery and motor vehicles.

However, it is noteworthy that Ativan showed no clinical evidence of accumulation even when given in high doses over periods up to 6 months. The half-life of free lorazepam is about 12 hours; steady-state serum levels are attained in 2-3 days. Comparable data for diazepam: 20-50 hours and at least 7-10 days. (The pharmacokinetic profile of a drug can define such characteristics as absorption, distribution, metabolism and elimination but cannot, at present, be directly related to its therapeutic effectiveness.)

Ativan has a convenient b.i.d. or t.i.d. dosage schedule; it is compatible with a long list of other medications and, of course, it is a highly effective anxiolytic agent, as established in numerous nationwide, double-blind, controlled evaluations in thousands of patients.

See important information on preceding page.

Ativan® (IV)
for (lorazepam)
Anxiety

High intensit
the ke

Trimpex (trimethoprim/Roche) diffuses and concentrates

Trimpex achieves high intensity concentrations in the urine—significantly greater levels than the MICs of susceptible urinary pathogens—a major reason for Trimpex high performance. Trimpex also diffuses into vaginal fluid at concentrations that inhibit coliform colonization of the vaginal introitus.

ROCHE®

concentrations—to high performance

95% overall efficacy

In controlled, comparative multiclinic studies, trimethoprim delivered a 95% overall cure rate (127 of 133 patients) seven days after completion of therapy.† The most common causative uropathogens were *E. coli, Klebsiella pneumoniae, Proteus mirabilis* and *Enterobacter* species.

Side effects generally infrequent and mild

At recommended dosage, the incidence of skin rash has been only 2.9%, with no reported incidence of diarrhea. In clinical studies which employed higher doses of Trimpex (trimethoprim/Roche), an elevated incidence of rash was noted. (See Adverse Reactions section of product summary.)

Safety considerations

Trimpex is contraindicated in patients hypersensitive to the drug and in patients with documented megaloblastic anemia due to folate deficiency. The benefits of Trimpex therapy during pregnancy and the nursing period should be weighed against the risks. Safe use in infants under 2 months and effectiveness in children under 12 years of age have not been established. (For further discussion of use in pregnancy, and other safety considerations, please see product summary on the following page of this advertisement.)

One small tablet B.I.D.—and it's economical

The convenient Trimpex dosage schedule—one small tablet twice a day for 10 days—is easier to follow than the Q.I.D. regimens of other agents. And Trimpex costs less than nitrofurantoin macrocrystals or any cephalosporin.

Performance • Convenience • Economy • Three good reasons to prescribe Trimpex for initial uncomplicated urinary tract infections.

†Data on file, Hoffmann-La Roche Inc.

95% EFFICACY WITH ONE SMALL TABLET TWICE A DAY.

Trimpex® 100-mg scored tablets

trimethoprim/ROCHE

FOR INITIAL EPISODES OF UNCOMPLICATED URINARY TRACT INFECTIONS*

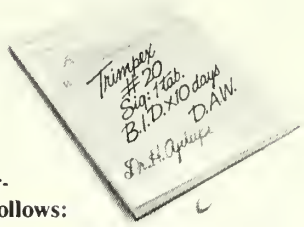
*due to susceptible strains of common uropathogens.

Before prescribing, please consult summary of product information on the following page.

95% efficacy with one small tablet twice a day

Trimpex®
trimethoprim/ROCHE

Diffuses and concentrates



Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS AND USE: For treatment of initial episodes of uncomplicated urinary tract infections due to susceptible strains of: *Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae* and *Enterobacter* species. Perform culture and susceptibility tests to determine bacterial susceptibility to trimethoprim. Therapy may be initiated prior to obtaining test results.

CONTRAINDICATIONS: Hypersensitivity to trimethoprim and in those with documented megaloblastic anemia due to folate deficiency.

WARNINGS: Occasional interference with hematopoiesis, especially when administered in large doses and/or for prolonged periods. Obtain CBC if early indications of serious blood disorders are noted; *i.e.*, sore throat, fever, pallor or purpura. Discontinue therapy if the count of any formed blood element is significantly reduced.

PRECAUTIONS: *General:* Give cautiously to patients with possible folate deficiency or those with impaired renal or hepatic function. Folates may be administered concomitantly without interfering with trimethoprim's antimicrobial action.

PREGNANCY

Category C: Because it may interfere with folic acid metabolism, use only during pregnancy if potential benefits justify the potential risk to the fetus.

Nursing Mothers: Because trimethoprim is excreted in human milk and may interfere with folic acid metabolism, exercise caution when administering Trimpex. *Pediatric Use:* Safety has not been demonstrated in infants under two months of age. Effectiveness not established in children under the age of 12.

ADVERSE REACTIONS: *Dermatologic Reactions:* Rash, pruritus and exfoliative dermatitis. At the recommended dose of 100 mg b.i.d., the incidence of rash is 2.9%. In clinical studies using high doses of Trimpex, a greater incidence of maculopapular, morbilliform, pruritic and generally mild to moderate rash was noted, appearing 7 to 14 days after therapy was initiated. *Gastrointestinal Reactions:* Epigastric distress, nausea, vomiting and glossitis. *Hematologic Reactions:* Thrombocytopenia, leukopenia, neutropenia, megaloblastic anemia and methemoglobinemia. *Miscellaneous Reactions:* Fever, elevation of serum transaminase and bilirubin, and increased BUN and serum creatinine levels.

DOSAGE AND ADMINISTRATION: Usual oral adult dosage: 100 mg Trimpex every 12 hours for 10 days.

In patients with a creatinine clearance of less than 15 ml/min, trimethoprim is not recommended. If creatinine clearance is between 15 to 30 ml/min, the dose should be 50 mg every 12 hours.

Effectiveness not established in children under the age of 12.

HOW SUPPLIED: Tablets, each containing 100 mg trimethoprim—bottles of 100; Tel-E-Dose® package of 100; Prescription Paks of 20.

ROCHE LABORATORIES
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

WESTERN SOCIETY OF ALLERGY AND IMMUNOLOGY

Presents

20th Annual Scientific Session

OCTOBER 22-24, 1981

HOTEL VANCOUVER
Vancouver, B.C., Canada

The Society is accredited for Category I of the American Medical Association Physician's Recognition Award by the LCCME.

There are 32 technical exhibit spaces available.

Additional information can be obtained from:
Mrs. Joyce M. Gullixson, Executive Secretary
Western Society of Allergy and Immunology
0324 S.W. Abernethy, Portland, OR 97201

Peralta Hospital Presents

CANCER UPDATE 1981

A Clinical Approach to the Management of Common Malignancies

Update on Interferon—Cancer of the Skin—Cancer of the Lung—Discussion of Tumor Markers—DES and Genital Cancer—Cancer of the Cervix

Friday, Jan. 23 and Saturday, Jan. 24, 1981

Goodman's Hall

10 Jack London Square
Oakland, CA

CANCER UPDATE 1981 is a 1½-day, no-fee seminar sponsored by Peralta Hospital, the medical staff and Peralta Medical Foundation. Nine hours of Formal Category I CME Credit offered. Pre-registration advisable.

Call or write for registration information

Education and Training Department
Peralta Hospital
450 Thirtieth Street
Oakland, CA 94609
(415) 451-4900

CONTINUING MEDICAL EDUCATION

California, Hawaii, Nevada • Alaska, Montana, Idaho • Oregon • Washington • Utah

CALIFORNIA, HAWAII and NEVADA

This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000, ext. 146. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

January 23-25—**Pediatric Anesthesiology—19th Clinical Conference.** Childrens Hospital of Los Angeles at Marriott Hotel, Los Angeles. 15 hrs. $165. Contact: Wayne Herbert, MD, P.O. Box 54700, Los Angeles 90054. (213) 669-2262.

March 14-21—**9th Obstetric Anesthesia Conference.** Ohio State Univ. at Sheraton Waikiki, Honolulu. One week. 25 hrs. Contact: Excursions Unlimited, Inc., c/o OSU Dept. of Anesthesiology, 1820 Northwest Blvd., Columbus, OH 43212. (800) 848-4438.

May 3-9—**17th Biennial Western Conference on Anesthesiology.** Hawaiian Regent Hotel, Waikiki (3-7) and Intercontinental Hotel, Maui (8-9). One week. 26 hrs. Contact: Biennial Western Conf. on Anesthesiology, Group Travel Unlimited, 700 Larkspur Landing Circle, Suite 169, Larkspur 94939.

CANCER

January 22-24—**Current Concepts in Cancer Diagnosis.** UCLA at Century Plaza Hotel, Los Angeles. Thursday-Saturday.

January 23-24—**Cancer Update 1981.** Peralta Hospital at Goodman's Hall, Jack London Square, Oakland. Friday-Saturday. 10 hrs. Contact: Susan Ford, Education and Training Dept., Peralta Hosp., 450 30th St., Oakland 94609. (415) 451-4900, ext. 2327.

January 24-25—**Current Approaches to Radiation Oncology.** UCSF at Sir Francis Drake Hotel, San Francisco. Saturday-Sunday.

January 30-February 1—**Midwinter Oncology Conference—for Radiation Oncologists.** L.A. Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. $150. Contact: John Kassabian, MD, 100 Congress St., Pasadena 91105.

February 5-9—**Controversies in Lung Cancer.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday-Monday. Contact: Program Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

February 10-13—**American Endocurietherapy Society—3rd Annual Midwinter Meeting.** Cal-Neva Lodge, North Lake Tahoe. Tuesday-Friday. 16 hrs. $150. Contact: AES, 5522 Sepulveda Blvd., Van Nuys 91411.

February 21—**Investigational Methods of Cancer Treatment.** San Francisco Unit, American Cancer Society, and San Francisco Regional Cancer Foundation at Fireman's Fund Building, San Francisco. Saturday. 4 hrs. $15. Contact: Terry Sheehy, PhD, S.F. Regional Cancer Fndn., 14th Ave. and Lake St., San Francisco 94118. (415) 221-2132.

February 23-26—**Advances in Clinical Practice of Hematology/Oncology.** See Medicine, February 23-26.

February 25—**Ovarian Cancer.** Hospital of the Good Samaritan at Hilton, Los Angeles. Wednesday. 7 hrs. Contact: Mary Jane Thompson, Hosp. of the Good Samaritan, 616 S. Witmer St., Los Angeles 90017. (213) 488-8908.

February 28-March 1—**Recent Advances in Cancer Diagnosis.** UCLA. Saturday-Sunday.

March 6-8—**Current Approaches to Radiation Oncology, Biology and Physics.** See Radiology, March 6-8.

March 8-13—**19th National Conference on Breast Cancer.** American College of Radiology, American Cancer Society, College of American Pathologists at Hotel del Coronado, Coronado. Sunday-Friday. 33 hrs. $275. Contact: ACR, 6900 Wisconsin Ave., Chevy Chase, MD 20015. (301) 654-6900.

March 13-14—**Childhood Cancer: Triumph Over Tragedy—16th Annual Cancer Symposium.** West Coast Cancer Foundation and Calif. Division of American Cancer Society at Hyatt Regency, San Francisco. Friday-Saturday. 12 hrs. $110 before February 1; $130 thereafter. Contact: WCCF, 50 Francisco St., Suite 200, San Francisco 94133. (415) 981-4590.

April 25—**Oncology Update: 1981.** Northridge Hospital at Century Plaza Hotel, Los Angeles. Saturday. 8 hrs. $125. Contact: Sandra Rozzen, Dept. of Med. Ed., Northridge Hosp., 18300 Roscoe Blvd., Northridge 91328. (213) 885-5311.

(Continued on Page 25)

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center 2801 Atlantic Ave., Long Beach 90801. (213) 595-3837.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Lolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

When she can't manage, you can.

The sweats. The hot flushes. The distress and discomfort of atrophic vaginitis. The possibility of osteoporosis.* The menopause.

For many women, it's a time of confusion and frustration. Counseling can help her overcome these feelings. But counseling *can't* stop vasomotor and vaginal symptoms, or retard bone loss*...the true signs of estrogen deficiency. And that's where she needs you most.

You're an expert at estrogen replacement. You know why it should be used. When it's best avoided. How to cycle therapy. Determine dosage. Check for contraindications and possible complications. Follow-up. You know when therapy should begin, and when it deserves to end.

Most of all, you know your patient—and when she needs the effective relief you can give her with PREMARIN.

When it comes to managing the estrogen-deficiency symptoms of the menopause, you've got what it takes.

*Conjugated Estrogens Tablets have been evaluated as probably effective for postmenopausal osteoporosis

Prescribed with care by physicians who care.

PREMARIN®
BRAND OF
CONJUGATED ESTROGENS TABLETS, U.S.P.
0.3 mg/0.625 mg/1.25 mg/2.5 mg

Please see following page for brief summary of prescribing information.

BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION, SEE PACKAGE CIRCULAR)

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA.

Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year[1-3] This risk was independent of the other known risk factors for endometrial cancer These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade[4] The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4 5 to 13 9 times greater than in nonusers The risk appears to depend on both duration of treatment[1] and on estrogen dose.[3] In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration,[3] it therefore appears prudent to utilize such a regimen. Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY

The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare[5,6] This risk has been estimated as not greater than 4 per 1000 exposures[7] Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis,[8-12] epithelial changes of the vagina and cervix Although these changes are histologically benign, it is not known whether they are precursors of malignancy Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects[13-16] One case control study[16] estimated a 4 7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion) Some of these exposures were very short and involved only a few days of treatment The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation

DESCRIPTION: PREMARIN (Conjugated Estrogens Tablets, U S P) for oral administration contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications for use as follows.

Effective:

1 Moderate to severe *vasomotor* symptoms associated with the menopause (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions)

2 Atrophic vaginitis

3 Kraurosis vulvae

4 Female hypogonadism

5 Female castration

6 Primary ovarian failure

7 Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease

8 Prostatic carcinoma—palliative therapy of advanced disease

9 Postpartum breast engorgement—Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens [19]

PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING)

"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures Final classification of this indication requires further investigation

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions: 1 Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease 2 Known or suspected estrogen-dependent neoplasia 3 Known or suspected pregnancy (See Boxed Warning) 4 Undiagnosed abnormal genital bleeding 5 Active thrombophlebitis or thromboembolic disorders. 6 A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy)

WARNINGS: At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast,[17] although a recent study has raised this possibility[18] There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens [17]

Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement, it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement [19-22] Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction [23-30] Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users [31,32] An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives [33,34] If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization Estrogens should not be used in persons with active thrombophlebitis, thromboembolic disorders, or in persons with a history of such disorders in association with estrogen use They should be used with caution in patients with cerebral vascular or coronary artery disease Large doses (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown[35] to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis When doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a clear risk

Benign hepatic adenomas should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives [36] Increased blood pressure may occur with use of estrogens in the menopause[37] and blood pressure should be monitored with estrogen use A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives For this reason, diabetic patients should be carefully observed Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases

PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed Conditions influenced by fluid retention such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc. Oral contraceptives appear to be associated with an increased incidence of mental depression.[23,38] Patients with a history of depression should be carefully observed Preexisting uterine leiomyomata may increase in size during estrogen use The pathologist should be advised of estrogen therapy when relevant specimens are submitted If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated Estrogens should be used with care in patients with impaired liver function, renal insufficiency metabolic bone diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete.

The following changes may be expected with larger doses of estrogen.

a Increased sulfobromophthalein retention

b Increased prothrombin and factors VII, VIII, IX, and X, decreased antithrombin 3, increased norepinephrine-induced platelet aggregability

c Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered

d Impaired glucose tolerance.

e Decreased pregnanediol excretion.

f Reduced response to metyrapone test

g Reduced serum folate concentration

h Increased serum triglyceride and phospholipid concentration

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives: breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhea, premenstrual-like syndrome, amenorrhea during and after treatment, increase in size of uterine fibromyomata, vaginal candidiasis, change in cervical erosion and in degree of cervical secretion; cystitis-like syndrome; tenderness, enlargement, secretion (of breasts), nausea, vomiting, abdominal cramps, bloating, cholestatic jaundice, chloasma or melasma which may persist when drug is discontinued, erythema multiforme; erythema nodosum, hemorrhagic eruption, loss of scalp hair, hirsutism, steepening of corneal curvature, intolerance to contact lenses, headache, migraine, dizziness, mental depression, chorea, increase or decrease in weight; reduced carbohydrate tolerance, aggravation of porphyria edema changes in libido

ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females

DOSAGE AND ADMINISTRATION: 1 *Given cyclically for short term use only* For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0.3 to 1.25 mg or more daily)

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible

Administration should be cyclic (e.g. three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals

2 *Given cyclically* Female hypogonadism Female castration. Primary ovarian failure. Osteoporosis

Female hypogonadism—2 5 to 7 5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration If bleeding does not occur by the end of this period, the same dosage schedule is repeated The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium.

If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U S P), 2 5 to 7 5 mg daily in divided doses, for 20 days During the last five days of estrogen therapy, give an oral progestin. If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding

Female castration and primary ovarian failure—1 25 mg daily, cyclically Adjust upward or downward according to response of the patient For maintenance, adjust dosage to lowest level that will provide effective control

Osteoporosis (to retard progression)—1 25 mg daily, cyclically

3 *Given for a few days* Prevention of postpartum breast engorgement—3 75 mg every four hours for five doses, or 1 25 mg every four hours for five days

4 *Given chronically* Inoperable progressing prostatic cancer—1 25 to 2 5 mg three times daily

Inoperable progressing breast cancer in appropriately selected men and postmenopausal women—10 mg three times daily for a period of at least three months

Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding

HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U S P) No. 865—Each *purple* tablet contains 2 5 mg in bottles of 100 and 1,000 No 866—Each *yellow* tablet contains 1 25 mg in bottles of 100 and 1,000 Also in unit dose package of 100 No 867—Each *red* tablet contains 0 625 mg in bottles of 100 and 1,000 Also in unit dose package of 100. No. 868—Each *green* tablet contains 0 3 mg in bottles of 100 and 1,000

PHYSICIAN REFERENCES: 1 Ziel, H K., *et al.* N Engl J Med *293*:1167-1170, 1975. 2. Smith, D C, *et al.*: N Engl J Med. *293*:1164-1167, 1975 3 Mack, TM, *et al.*: N Engl J Med *294*:1262-1267, 1976 4 Weiss, N S, *et al.*: N Engl J Med *294*:1259-1262, 1976 5 Herbst, A L, *et al.*: N Engl J Med *284*:878-881, 1971 6 Greenwald, P, *et al.*: N Engl J Med *285*:390-392, 1971 7 Lanier, A, *et al.*: Mayo Clin. Proc *48*:793-799, 1973 8. Herbst, A., *et al.*: Obstet Gynecol *40*:287-298, 1972 9 Herbst, A., *et al.* Am J Obstet Gynecol *118*:607-615, 1974 10 Herbst, A, *et al.* N Engl J Med. *292*:334-339, 1975 11 Staff, A, *et al.* Obstet Gynecol. *43*:118-128, 1974 12 Sherman, A I, *et al.* Obstet Gynecol. *44*:531-545, 1974 13 Gal, I, *et al.* Nature *216*:83, 1967 14 Levy, E P, *et al.* Lancet *1*:611, 1973 15 Nora, J., *et al.* Lancet *1*:941-942, 1973 16 Janerich, D T, *et al.* N Engl J Med *291*:697-700, 1974 17 Boston Collaborative Drug Surveillance Program N Engl J Med *290*:15-19, 1974 18 Hoover, R, *et al.* N Engl J Med *295*:401-405, 1976 19 Daniel, D. G, *et al.*: Lancet *2*:287-289, 1967 20 The Veterans Administration Cooperative Urological Research Group: J. Urol *98*:516-522, 1967 21 Bailar, J C Lancet *2*:560, 1967 22 Blackard, C., *et al.*: Cancer *26*:249-256, 1970 23 Royal College of General Practitioners: J R Coll Gen. Pract. *13*:267-279, 1967 23a Royal College of General Practitioners. Oral Contraceptives and Health, New York, Pitman Corp., 1974 24 Inman, W H W, *et al.*: Br Med J. *2*:193-199, 1968 25. Vessey, M P, *et al.* Br Med J *2*:651-657, 1969 26. Sartwell, P E., *et al.*: Am J Epidemiol. *90*:365-380, 1969 27. Collaborative Group for the Study of Stroke in Young Women. N Engl J Med *288*:871-878, 1973 28 Collaborative Group for the Study of Stroke in Young Women. J A M A *231*:718-722, 1975 29. Mann, J I., *et al.*: Br Med J *2*:245-248, 1975 30. Mann, J I., *et al.* Br Med J *2*:241-245, 1975 31. Inman, W H W, *et al.*: Br Med J *2*:203-209, 1970 32. Stolley, P D., *et al.* Am J Epidemiol *102*:197-208, 1975 33 Vessey, M P, *et al.* Br Med J *3*:123-126, 1970 34 Greene, G R, *et al.* Am J Public Health *62*:680-685, 1972 35 Coronary Drug Project Research Group J A M A *214*:1303-1313, 1970 36 Mays, E T., *et al.*: J A M A *235*:730-732, 1976 37 Pfeffer, R I., *et al.* Am J Epidemiol *103*:445-456, 1976

7457/181

Ayerst AYERST LABORATORIES
New York, N.Y. 10017

(Continued from Page 21)

May 18-22—**Medical Oncology Review.** American College of Physicians at University of Hawaii School of Medicine, Honolulu. Monday-Friday. Contact: Postgraduate Dept., ACP, 4200 Pine St., Philadelphia, PA 19104. (215) 243-1200.

EMERGENCY MEDICINE

January 19-23—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

January 19-23—**Postgraduate Institute for Emergency Room Physicians, Symposium I.** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $425.

January 21-23—**Sierra Traumatological Society.** See Surgery, January 21-23.

January 23-25—**Advanced Cardiac Life Support Workshops.** Emergency Medical Systems, Inc., at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact: EMS, 2310 Mason St., San Francisco 94133. (415) 956-5900.

February 16-19—**Emergency Medicine: New Concepts in Resuscitation.** UCD at Hyatt Lake Tahoe, Incline Village. Monday-Thursday. 19¼ hrs.

February 16-20—**Postgraduate Institute for Emergency Room Physicians, Symposium III.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $425.

March 8-14—**2nd Annual Mammoth Mountain Emergency Medicine Ski Conference.** UCI at Mammoth Mountain. One week. 25 hrs. $290. Contact: Daniel Abbott, MD, P.O. Box 52-B, Newport Beach 92662. (714) 642-7080.

March 23-27—**Postgraduate Institute for Emergency Room Physicians, Symposium II.** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $425.

April 18-25—**Emergency Medical Care.** Univ. of Washington School of Medicine at Wailea Beach, Maui. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

April 24-26—**Advanced Cardiac Life Support Workshops.** Emergency Medical Systems at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact. EMS, 2310 Mason St., San Francisco 94133. (415) 956-5900.

April 25-May 2—**Emergency Medicine.** USC at Royal Lahaina Hotel, Maui. One week. $350.

May 4-8—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $425.

May 7-9—**Cardiovascular Emergencies.** See Medicine, May 7-9.

May 13—**Emergency Medicine.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6 hrs. $35. Contact: Cont. Med. Ed., N. T. Enloe Mem. Hosp., 5th Ave. and The Esplanade, Chico 95926. (800) 822-8102, ext. 7375.

Emergency Medicine Grand Rounds. Herrick Hospital and Health Center, Berkeley. 2nd Wednesday of each month; 12:00-1:00 p.m. Cat. I—CMA, AMA, ACEP. Free, including lunch. January 14—Mast Suit (Neumatic Shock Trousers): Use, Principles and Demonstration. February 11—Early Care in Management of Burns. Contact: James Simon, MD, Emergency Med. Dept., Herrick Hosp. and Health Ctr., 2001 Dwight Way, Berkeley 94705. (415) 540-4555.

MEDICINE

January 23-24—**2nd Clinical Conference on Congenital Heart Disease.** Childrens Hospital of Los Angeles at Biltmore Hotel, Los Angeles. Friday-Saturday. 12 hrs. Contact: Bernard L. Tucker, MD, 1136 W. 6th St., Los Angeles 90017.

January 23-24—**8th Annual Allergy/Immunology Symposium —Challenges in Allergic and Immunologic Disorders.** Southern Calif. Permanente Medical Group at Hilton, Pasadena. Friday-Saturday. Contact: Shirley Gach, SCPMG, Education and Research, 4747 Sunset Blvd., 4th Fl., Los Angeles 90027. (213) 667-4241.

January 24—**Cardiology Seminar—10th Annual.** Fresno Community Hospital and Medical Center. Saturday. Contact: Joann Ellis, Ed. and Training Dept., Fresno Community Hosp., P.O. Box 1232, Fresno 93715. (209) 442-6000, ext. 5696.

January 26-28—**Practical Management of Bronchial Asthma.** Scripps Clinic and Research Foundation at Vacation Village, San Diego. Monday-Wednesday. 20 hrs. $265. Contact: Nomi Feldman, 2321 Morena Blvd., San Diego 92110. (714) 275-0650.

January 28—**A Closer Look at Prevention and Management of Stroke.** American Heart Assn., Santa Clara Co. Chap., at LeBaron Hotel, San Jose. Wednesday. 5 hrs. $35. Contact: Harriet M. Schutte, RN, PhD, AHA, 3003 Moorpark Ave., San Jose 95128. (408) 247-8555.

January 30-31—**Cardiology Update — 1981 — The Changing Scene.** St. Francis Medical Center at Bonaventure Hotel, Los Angeles. Friday-Saturday. 14 hrs. Contact: Allan Hoffman, EdD, Dir. of Med. Ed., St. Francis Med. Ctr., 3630 Imperial Highway, Lynwood 90262. (213) 603- 6174.

January 30-February 1—**Cardiac Ischemia and Arrhythmias—Current Concepts for Diagnosis and Treatment.** International Medical Education Corp. at Aladdin Hotel, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

February 2-4—**Clinical Echocardiography—1981.** American College of Cardiology at Sheraton Harbor Island Hotel, San Diego. Monday-Wednesday. Contact: Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

February 4—**Endocrine Disorders.** St. Francis Medical Center, Lynwood. Wednesday. 6 hrs. Contact: Allan M. Hoffman, EdD, Dir. of Med. Ed., St. Francis Med. Ctr., 3630 Imperial Highway, Lynwood 90262. (213) 603-6174.

February 4-6—**Children With Heart Disease.** USC at Gene Autry Hotel, Palm Springs. Wednesday-Friday. 14 hrs.

February 4-6—**Western Section of the Society for Investigative Dermatology, Western Section of American Federation for Clinical Research, Western Society for Clinical Research.** Carmel. Wednesday-Friday. Contact: Charles B. Slack, Inc., 6900 Grove Rd., Thorofare, NJ 08086.

February 11-13—**Recent Advances in Neurology.** UCSF. Wednesday-Friday.

February 14—**Sixth Annual Liver Conference: Cirrhosis.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Saturday. 7 hrs. Contact: Program Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

February 16-18—**Recent Advances in Clinical Endocrinology.** UCSF at Sir Francis Drake Hotel, San Francisco. Monday-Wednesday.

February 17-20—**Epilepsy in Childhood and Adolescence—32nd Annual Western Institute on Epilepsy.** Univ. of Nevada School of Medicine, Reno. Tuesday-Friday. Contact: Cont. Med. Ed., College Inn, Univ. of Nevada, Reno 89557.

February 18-20—**Neuro-Orthopedic Screening.** UCSD at Vacation Village, San Diego. Wednesday-Friday.

February 18-April 22—**Gastroenterology.** UCLA. Wednesday evenings.

February 19-22—**Federation of Western Societies of Neurological Science.** Stanford Court, San Francisco. Thursday-Sunday. Contact: Grant E. Gauger, MD, 1411 E. 31st St., Oakland 94602.

February 19-23—**Sacramento Valley Dermatological Society—Annual Winter Seminar.** North Lake Tahoe. Thursday-Monday. 20 hrs. Contact: Sacramento Valley Dermatological Society, c/o Dr. Bock, 1502 St. Marks Plaza, Stockton 95207.

February 20-22—**Pathophysiology and Techniques of Cardiopulmonary Bypass.** Cardiothoracic Research and Education

(Continued on Page 45)

for your patients with moderate depression and anxiety

RELIEF WITHOUT A

The choice without a phenothiazine

☐ provides the specifically effective antianxiety action of Librium® (chlordiazepoxide HCl/Roche), with its outstanding safety record, together with the well established antidepressant effect of amitriptyline.

☐ symptoms likely to respond in the first week of treatment include insomnia, anorexia, psychic and somatic anxiety, agitation and feelings of guilt or worthlessness.

A better choice because

☐ minimizes risk of tardive dyskinesia and other extrapyramidal side effects. The causal relationship between the phenothiazines and extrapyramidal side effects, including tardive dyskinesia, is well established. In contrast, the reported incidence of these adverse reactions with Limbitrol or either of its components is rare.

ROCHE®

PHENOTHIAZINE

What better reason to switch from a phenothiazine combination and start prescribing

Limbitrol® IV

Tablets 5-12.5 each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)

Tablets 10-25 each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt)

Please see following page for summary of product information.

LIMBITROL® TABLETS Tranquilizer—Antidepressant

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Relief of moderate to severe depression associated with moderate to severe anxiety

Contraindications: Known hypersensitivity to benzodiazepines or tricyclic antidepressants. Do not use with monoamine oxidase (MAO) inhibitors or within 14 days following discontinuation of MAO inhibitors since hyperpyretic crises, severe convulsions and deaths have occurred with concomitant use; then initiate cautiously, gradually increasing dosage until optimal response is achieved. Contraindicated during acute recovery phase following myocardial infarction.

Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients. (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

***Usage in Pregnancy:* Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage; withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline, symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).

Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. Concomitant use with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy.

Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.

Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.

The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs:

Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.

Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido.

Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.

Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.

Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.

Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.

Endocrine: Testicular swelling and gynecomastia in the male; breast enlargement, galactorrhea and minor menstrual irregularities in the female and elevation and lowering of blood sugar levels.

Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single h.s. dose may suffice for some patients. Lower dosages are recommended for the elderly.

Limbitrol 10-25, initial dosage of three to four tablets daily in divided doses, increased up to six tablets or decreased to two tablets daily as required. Limbitrol 5-12.5, initial dosage of three to four tablets daily in divided doses, for patients who do not tolerate higher doses.

How Supplied: White, film-coated tablets, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt) and blue, film-coated tablets, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt). Bottles of 100 and 500, Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10; Prescription Paks of 50.

ROCHE®

ROCHE PRODUCTS INC
Manati, Puerto Rico 00701

Your guide to patient management... when you decide medication is needed

How to initiate and maintain therapy

Select dosage strength appropriate for each patient

- Limbitrol 5-12.5 is recommended to minimize drowsiness and for elderly patients
- Limbitrol 10-25 may be indicated for patients who tolerate medication without undue side effects

Specify daily dosage based on symptom severity

- An initial dosage of three tablets is recommended
- Dosage may be increased to six tablets or decreased to two tablets daily as necessary
- Once a satisfactory response is obtained, patients should be continued on the smallest dose required to maintain the desired effect

Utilize dosage options to best accommodate individual patient needs

- T.I.D. or Q.I.D., familiar regimens most suited for patients who tolerate medication without undue drowsiness
- Two tablets one hour before bedtime and one tablet midday may minimize daytime drowsiness and help relieve a common target symptom — insomnia
- Entire dosage h.s. to take maximum advantage of the sedative effect

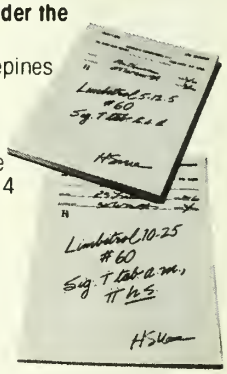
How to make each patient an informed patient

1. Discuss with patients the probability that they will experience drowsiness, especially during the first week.
2. Reassure your patients that drowsiness is one indication that the medication is working and that it may help alleviate their insomnia.
3. Encourage patients to report if drowsiness becomes troublesome so that, if necessary, dosage schedule can be adjusted.
4. Caution patients about the combined effects with alcohol or other CNS depressants. Let them know that the additive effects may produce a harmful level of sedation and CNS depression.
5. Caution patients about activities requiring complete mental alertness, such as operating machinery or driving a car.
6. Warn pregnant patients and patients of childbearing age that the safety of Limbitrol in pregnancy has not yet been established.

Please see complete product disclosure for other pertinent information.

Limbitrol should not be used under the following circumstances:

1. Hypersensitivity to benzodiazepines or tricyclic antidepressants.
2. Concomitantly with an MAO inhibitor. To replace an MAO inhibitor with Limbitrol, discontinue MAO inhibitor for a minimum of 14 days before cautiously initiating Limbitrol therapy.
3. During the acute recovery phase following myocardial infarction.



In moderate depression and anxiety

Limbitrol® IV

Relief without a phenothiazine

works well in your office...

NEOSPORIN® Ointment

(polymyxin B-bacitracin-neomycin)

Each gram contains: Aerosporin® (Polymyxin B Sulfate) 5,000 units, bacitracin zinc 400 units, neomycin sulfate 5 mg (equivalent to 3.5 mg neomycin base); special white petrolatum qs; in tubes of 1 oz and 1/2 oz and 1/32 oz (approx.) foil packets.

works just as well in their homes.

- It's effective therapy for abrasions, lacerations, open wounds, primary pyodermas, secondarily infected dermatoses.
- It provides broad-spectrum overlapping antibacterial effectiveness against common susceptible pathogens, including staph and strep.

- It helps prevent topical infections, and treats those that have already started.
- It contains three antibiotics that are rarely used systemically.
- It is convenient to recommend without a prescription.

NEOSPORIN® Ointment—for the office, for the home.
(polymyxin B-bacitracin-neomycin)

Effective • Economical • Convenient • Recommendable

Each gram contains: Aerosporin® (Polymyxin B Sulfate) 5,000 units, bacitracin zinc 400 units, neomycin sulfate 5 mg (equivalent to 3.5 mg neomycin base); special white petrolatum qs; in tubes of 1 oz and 1/2 oz and 1/32 oz (approx.) foil packets.

WARNING: Because of the potential hazard of nephrotoxicity and ototoxicity due to neomycin, care should be exercised when using this product in treating extensive burns, trophic ulceration and other extensive conditions where absorption of neomycin is possible. In burns where more than 20 percent of the body surface is affected, especially if the patient has impaired renal function or is receiving other aminoglycoside antibiotics concurrently, not more than one application a day is recommended.

When using neomycin-containing products to control secondary infection in the chronic dermatoses, it should be borne in mind that the skin is more liable to become sensitized to many substances, including neomycin. The manifestation of sensitization to neomycin is usually a low grade reddening with swelling, dry scaling and itching; it may be manifest simply as a failure to heal. During long-term use of neomycin-containing products, periodic examination for such signs is advisable and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for that patient thereafter.

PRECAUTIONS: As with other antibacterial preparations, prolonged use may result in overgrowth of non-susceptible organisms, including fungi. Appropriate measures should be taken if this occurs.

ADVERSE REACTIONS: Neomycin is a not uncommon cutaneous sensitizer. Articles in the current literature indicate an increase in the prevalence of persons allergic to neomycin. Ototoxicity and nephrotoxicity have been reported (see Warning section).

Complete literature available on request from Professional Services Dept. PML.

Wellcome

Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

SPOT-RESISTANT ORAL CONTRACEPTION IS HERE!

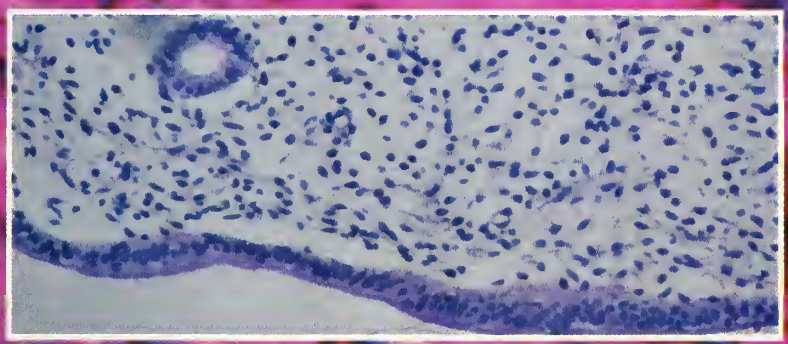
It's LO/OVRAL 30. And here's how it holds spotting and breakthrough bleeding to a minimum: Hormone balance right from the start...and throughout the cycle. Hormone balance made possible with a very low dose oral contraceptive because of the supportive progestational activity of norgestrel, Wyeth's exclusive progestogen.

Regular withdrawal bleeding, too despite its low dose. In clinical trials amenorrhea—defined as absence of bleeding in the 7 pill-free days—was reported in only 2.1% of total cycles. And when defined as absence of bleeding for 60 days or more (as it often is), the incidence was only 0.2%.*

And comfort for most patients* thanks to the same balance that helps prevent spotting and breakthrough bleeding. In the clinical trials, most patients stayed free of common side effects such as nausea (0.6% of cycles), vomiting (0.1%), depression (0.5%) and acne (0.9%).

Wyeth Laboratories
Philadelphia, Pa 19101

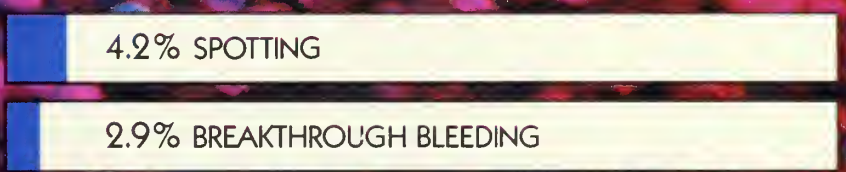
Copyright © 1980, Wyeth Laboratories. All rights reserved.



LO/OVRAL—1st cycle
Biopsy of intact endometrium in stable, progestogen suppressed state. Small, tubular gland in loose stroma without hemorrhage, fragmentation or debris characteristic of desquamating endometrium.

Even in the first cycle, the effective action of LO/OVRAL on the endometrium, such as you see here, provides the resistance against spotting and breakthrough bleeding you hope to achieve.

HISTOLOGICALLY... AND CLINICALLY.



A near-spotless record— in clinical trials involving 22,489 cycles*

*Serious as well as minor adverse reactions have been reported following the use of all oral contraceptives. Contraindications, Warnings, Precautions, Adverse Reactions, etc., in the accompanying In Brief should be carefully considered.

See full prescribing information.

LO/OVRAL® 30 mcg

each tablet contains 0.3 mg norgestrel with 0.03 mg ethinyl estradiol, Wyeth

...with a near-spotless record!

See important information on following page.

IN BRIEF:

Indications and Usage—LO/OVRAL® is indicated for the prevention of pregnancy in women who elect to use oral contraceptives (OC's) as a method of contraception.

Contraindications—OC's should not be used in women with any of the following conditions: 1. Thrombophlebitis or thromboembolic disorders. 2. A past history of deep-vein thrombophlebitis or thromboembolic disorders 3. Cerebral-vascular or coronary-artery disease. 4. Known or suspected carcinoma of the breast 5. Known or suspected estrogen-dependent neoplasia 6. Undiagnosed abnormal genital bleeding 7. Known or suspected pregnancy (see Warning No. 5). 8. Benign or malignant liver tumor which developed during use of OC's or other estrogen-containing products

Warnings

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious conditions, including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

1. *Thromboembolic Disorders and Other Vascular Problems*—An increased risk of thromboembolic and thrombotic disease associated with use of OC's is well established. Three principal studies in Great Britain and 3 in the U.S. have demonstrated increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic. These studies estimate that users of OC's are 4 to 11 times more likely than nonusers to develop these diseases without evident cause.

CEREBROVASCULAR DISORDERS—In a collaborative American study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than nonusers and the risk of thrombotic stroke was 4 to 9.5 times greater in users than in nonusers.

MYOCARDIAL INFARCTION (MI)—An increased risk of MI associated with use of OC's has been reported, confirming a previously suspected association. These studies, conducted in the UK, found, as expected, that the greater the number of underlying risk factors for coronary artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of pre-eclamptic toxemia) the higher the risk of developing MI, regardless of whether the patient was an OC user or not. OC's, however, were found to be a clear additional risk factor. In terms of relative risk, it has been estimated that OC users who do not smoke (smoking is considered a major predisposing condition to MI) are about twice as likely to have a fatal MI as nonusers who do not smoke. OC users who are also smokers have about a 5-fold increased risk of fatal MI compared to users who do not smoke, but about a 10- to 12-fold increased risk compared to nonusers who do not smoke. Furthermore, amount of smoking is also an important factor. In determining importance of these relative risks, however, baseline rates for various age groups must be given serious consideration. Importance of other predisposing conditions mentioned above in determining relative and absolute risks has not as yet been quantified; quite likely the same synergistic action exists, but perhaps to a lesser extent.

RISK OF DOSE—In an analysis of data derived from several national adverse-reaction reporting systems, British investigators concluded that risk of thromboembolism, including coronary thrombosis, is directly related to dose of estrogen in OC's. Preparations containing 100 mcg or more of estrogen were associated with higher risk of thromboembolism than those containing 50-80 mcg. Their analysis did suggest, however, that quantity of estrogen may not be the sole factor involved. This finding has been confirmed in the U.S.

ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASES—A large prospective study carried out in the UK estimated the mortality rate per 100,000 women per year from diseases of the circulatory system for users and nonusers of OC's according to age, smoking habits, and duration of use. Overall excess death rate annually from circulatory diseases for OC users was estimated to be 20 per 100,000 (ages 15-34—5/100,000; ages 35-44—33/100,000; ages 45-49—140/100,000), risk being concentrated in older women, in those with long duration of use, and in cigarette smokers. It was not possible, however, to examine interrelationships of age, smoking, and duration of use, nor to compare effects of continuous vs. intermittent use. Although the study showed a 10-fold increase in death due to circulatory diseases in users for 5 or more years, all these deaths occurred in women 35 or older. Until larger numbers of women under 35 with continuous use for 5 or more years are available, it is not possible to assess magnitude of relative risk for this younger group. Available data from a variety of sources have been analyzed to estimate risk of death associated with various methods of contraception. Estimates of risk of death for each method include combined risk of contraceptive method (e.g., thromboembolic and thrombotic disease in the case of OC's) plus risk attributable to pregnancy or abortion in event of method failure. This latter risk varies with effectiveness of method. The study concluded that mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of OC's in women over 40 who smoke. Lowest mortality is associated with condom or diaphragm backed up by early abortion. Risk of thromboembolic and thrombotic disease associated with OC's increases with age after about 30 and, for MI, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of pre-eclamptic toxemia, and especially cigarette smoking. Physician and patient should be alert to earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

A 4- to 6-fold increased risk of postsurgery thromboembolic complications has been reported in OC users.

If feasible, OC's should be discontinued at least 4 weeks before surgery of a type associated with increased risk of thromboembolism or prolonged immobilization.

2. *Ocular Lesions*—There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis associated with use of OC's. Discontinue OC's if there is unexplained, sudden or gradual, partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal-vascular lesions, and institute appropriate diagnostic and therapeutic measures.

3. *Carcinoma*—Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases frequency of carcinoma of the breast, cervix, vagina, and liver. Certain synthetic progestogens, none currently contained in OC's, have been noted to increase incidence of mammary nodules, benign and malignant, in dogs. In humans, 3 case-control studies have reported an increased risk of endometrial carcinoma associated with prolonged use of exogenous estrogen in postmenopausal women. One publication reported on the first 21 cases submitted by physicians to a registry of cases of adenocarcinoma of the endometrium in women under 40 on OC's. Of cases found in women without predisposing risk factors (e.g., irregular bleeding at the time OC's were first given, polycystic ovaries), nearly all occurred in women who had used a sequential OC. These are no longer marketed. No evidence has been reported suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only OC's. Several studies have found no increase in breast cancer in women taking OC's or estrogens. One study, however, while also noting no overall increased risk of breast cancer in women on OC's, found an excess risk in subgroups of OC users with documented benign breast disease. Reduced occurrence of benign breast tumors in users of OC's has been well documented. In summary, there is at present no confirmed evidence from human studies of increased risk of cancer associated with OC's. Close clinical surveillance of all women on OC's is, nevertheless, essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer or with breast nodules, fibrocystic disease, or abnormal mammograms should be monitored with particular care if they elect to use OC's.

4. *Hepatic Tumors*—Benign hepatic adenomas have been found to be associated with use of OC's. One study showed that OC's with high hormonal potency were associated with higher risk than lower potency OC's. Although benign, hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage. This has been reported in short-term as well as long-term users. Two studies relate risk with duration of use of OC's, the risk being much greater after 4 or more years' use. While hepatic adenoma is rare, it should be considered in women presenting abdominal pain and tenderness, abdominal mass or shock. A few cases of hepatocellular carcinoma have been reported in women on OC's. Relationship of these drugs to this type of malignancy is not known.

5. *Use in or Immediately Preceding Pregnancy, Birth Defects in Offspring, and Malignancy in Female Offspring*—Use of female sex hormones—both estrogenic and progestational agents—during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, have increased risk of developing in later life a form of vaginal or cervical cancer ordinarily extremely rare. This risk has been estimated to be of the order of 1 in 1,000 exposures or less. Although there is no evidence now that OC's further enhance risk of developing this type of malignancy, such patients should be monitored with particular care if they elect to use OC's. Furthermore, 30 to 90% of such exposed women have been found to have epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether this condition is a precursor of vaginal malignancy. Male children so exposed may develop abnormalities of the urogenital tract. Although similar data are not available with use of other estrogens, it cannot be presumed they would not induce similar changes. An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with use of sex hormones, including OC's, in pregnancy. One case-control study estimated a 4.7-fold increase in risk of limb-reduction defects in infants exposed in utero to sex hormones (OC's, hormonal withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some exposures involved only a few days. Data suggest that risk of limb-reduction defects in exposed fetuses is somewhat less than 1 in 1,000 live births. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective. There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing OC's. Embryos with these anomalies are virtually always aborted spontaneously. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping OC's is unknown. It is recommended that, for any patient who has missed 2 consecutive periods, pregnancy should be ruled out before continuing OC's. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at time of first missed period, and further use of OC's should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus, and advisability of continuation of the pregnancy should be discussed. It is also recommended that women who discontinue OC's with intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive. Many clinicians recommend 3 months, although no precise information is available on which to base this. The administration of progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy.

6. *Gallbladder Disease*—Studies report increased risk of surgically confirmed gallbladder disease in users of OC's and estrogens. In one study, increased risk appeared after 2 years' use and doubled after 4 or 5 years' use. In one of the other studies, increased risk was apparent between 6 and 12 months' use.

7. *Carbohydrate and Lipid Metabolic Effects*—Decrease in glucose tolerance has been observed in a significant percentage of patients on OC's. For this reason, prediabetic and diabetic patients should be carefully observed while on OC's. Increase in triglycerides and total phospholipids has been observed in patients on OC's; clinical significance of this finding remains to be defined.

8. *Elevated Blood Pressure*—Increase in blood pressure has been reported in patients on OC's. In some women, hypertension may occur within a few months of beginning OC's. In the 1st year of use, prevalence of women with hypertension is low in users and may be no higher than that of a comparable group of nonusers. Prevalence in users increases, however, with longer exposure, and in the 5th year of use is 2½ to 3 times the reported prevalence in the 1st year. Age is also strongly correlated with development of hypertension in OC users. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure on OC's. Hypertension that develops as a result of taking OC's usually returns to normal after discontinuing the drug.

9. *Headache*—Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of OC's and evaluation of the cause.

10. *Bleeding Irregularities*—Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing OC's. In breakthrough bleeding, as in all cases of irregular vaginal bleeding, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or change to another OC may solve the problem. Changing to an OC with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary, since this may increase risk of thromboembolic disease. Women with past history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrheic after discontinuing OC's. Women with these pre-existing problems should be advised of this possibility and encouraged to use other methods. Post-use anovulation, possibly prolonged, may also occur in women without previous irregularities.

11. *Ectopic Pregnancy*—Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

12. *Breast-feeding*—OC's given in the postpartum period may interfere with lactation and decrease quantity and quality of breast milk. Furthermore, a small fraction of the hormones in OC's has been identified in the milk of mothers on OC's, effects, if any, on the breast-fed child have not been determined. If feasible, defer OC's until infant has been weaned.

Precautions—GENERAL—1. A complete medical and family history should be taken prior to initiation of OC's. Pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Pap smear and relevant laboratory tests. As a general rule OC's should not be prescribed for longer than 1 year without another physical examination.

2. Under influence of estrogen-progestogen preparations, pre-existing uterine leiomyomata may increase in size.

3. Patients with history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while on OC's should stop OC's and use an alternate method to try to determine whether the symptom is drug-related.

4. OC's may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, asthma, or cardiac or renal insufficiency.

5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence while on OC's. If jaundice develops, OC's should be discontinued.

6. Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution.

7. OC users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency. Clinical significance is undetermined.

8. Serum folate levels may be depressed by OC's. Since the pregnant woman is predisposed to development of folate deficiency and incidence of folate deficiency increases with increasing gestation, it is possible that if a woman becomes pregnant shortly after stopping OC's, she may have a greater chance of developing folate deficiency and complications attributed to this deficiency.

9. The pathologist should be advised of OC therapy when relevant specimens are submitted.

10. Certain endocrine- and liver-function tests and blood components may be affected by estrogen-containing OC's: a. Increased sulfobromophthalein retention. b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. c. Increased thyroid-binding globulin (TBG) leading to increased circulating total-thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered. d. Decreased pregnanediol excretion. e. Reduced response to metyrapone test.

Information for the Patient—See Patient Package Labeling.

Drug Interactions—Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin. A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, ampicillin and tetracycline.

Carcinogenesis—See Warnings on carcinogenic potential of OC's.

Pregnancy—Category X. See Contraindications, Warnings.

Nursing Mothers—See Warnings.

Adverse Reactions—An increased risk of these serious adverse reactions has been associated with use of OC's (see Warnings): thrombophlebitis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, cerebral hemorrhage, hypertension, gallbladder disease, benign hepatomas, congenital anomalies. There is evidence of an association between the following conditions and use of OC's although additional confirmatory studies are needed: mesenteric thrombosis, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions have been reported in patients on OC's and are believed to be drug-related: Nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10 percent or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally: Gastrointestinal symptoms (such as abdominal cramps and bloating); breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea, amenorrhea during and after treatment, temporary infertility after discontinuance of treatment; edema; chloasma or melasma which may persist, breast changes: tenderness, enlargement, and secretion; change in weight (increase or decrease); change in cervical erosion and cervical secretion; possible diminution in lactation when given immediately postpartum; cholestatic jaundice; migraine; increase in size of uterine leiomyomata; rash (allergic); mental depression; reduced tolerance to carbohydrates; vaginal candidiasis; change in corneal curvature (steepening), intolerance to contact lenses.

The following adverse reactions have been reported in users of OC's, and the association has been neither confirmed nor refuted: premenstrual-like syndrome, cataracts, changes in libido, chorea, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, vaginitis, porphyria.

Acute Overdose—Serious ill effects have not been reported following acute ingestion of large doses of OC's by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

LO/OVRAL® each tablet contains 0.3 mg norgestrel with 0.03 mg ethinyl estradiol.

Wyeth Laboratories Phila., Pa 19101

THE WESTERN
Journal of Medicine

Refer to: Kishpaugh KK, Ford MH, Castle CH, et al: Myocardial infarction: A five-year follow-up of patients. West J Med 134:1-6, Jan 1981

Myocardial Infarction: A Five-Year Follow-up of Patients

KARLA K. KISHPAUGH; MARILYN H. FORD, MS; C. HILMON CASTLE, MD, *and* JAMES C. READING, PhD, *Salt Lake City*

Patients with acute myocardial infarction (2,020) admitted to coronary care units (CCU) in Utah were studied for five years. Of these, 1,641 (81.4 percent) survived to leave the hospital. The male to female ratio was 3.5:1. At four months, one year and yearly thereafter from the date of admission to CCU, patients were mailed follow-up questionnaires. Cause of death was obtained from autopsy reports and death certificates. Patients were grouped yearly by the number of cardiac symptoms reported. Of patients discharged whose cases were followed, 925 (61.9 percent) were alive after five years. Reinfarction was the major cause of death in the hospital; however, during follow-up only 36.8 percent of deaths were attributable to myocardial infarction. At follow-up after a year, fewer cardiac symptoms were reported by patients who survived to the fifth year of follow-up than by patients who did not. Women were older and showed a higher death rate during follow-up. Increasing age was found to be a determining factor in long-term mortality after acute myocardial infarction.

IMPROVEMENTS IN THE diagnosis and treatment of acute myocardial infarction (AMI) in recent years have resulted in a need for reevaluation of current assumptions regarding long-term morbidity and mortality. Early studies of mortality in patients with myocardial infarction (MI) did not, for example, employ consistent criteria for diagnosis,[1-3] and patients included in these studies had a variety of health problems. With an emphasis on and improvements in coronary care in the 1960's, and with the introduction of new cardiac enzyme assays, it is possible to define more precisely a study group that meets established criteria for AMI.

In recent years, there has been a decrease in mortality of patients in hospital during the acute phases of illness[4-6] because of improved treatment methods and more extensive use of coronary care units (CCU). Consequently, a larger proportion of AMI patients now survive and are discharged. Improvement in early survival after an infarction accentuates the need for physicians to know those factors which affect long-term prognosis of patients with ischemic heart disease. Moreover, previous studies have emphasized primarily the importance of risk factors and complications in the

From the Department of Family and Community Medicine, University of Utah College of Medicine, Salt Lake City.

Submitted, revised, August 15, 1980.

Reprint requests to: C. Hilmon Castle, MD, 1C 303, Medical Center, Department of Family/Community Medicine, University of Utah, Salt Lake City, UT 84132.

ABBREVIATIONS USED IN TEXT

AMI = acute myocardial infarction
CCU = coronary care unit
MI = myocardial infarction

acute phase of illness in order to develop prognostic indices.[7-9]

Many investigators have reported death rates for AMI patients who were followed from 3 to 25 years,[1-3,10-23] but few recent studies in this country have dealt with the more subjective problems of discomfort, disability and dissatisfaction that are associated with myocardial infarction.[14,17,19] The purpose of our study is to compare women and men with regard to long-term mortality, using data obtained from records of 2,020 patients admitted to hospital with AMI and 1,495 men and women from this group who were discharged from the hospital and followed for five years.

Methods

Study Group

Twelve Utah hospitals participated in a program for assessing the quality of care provided to AMI patients from January 1970 through December 1972. The conditions of all patients admitted to a participating CCU were categorized into four groups: definite, probable, possible or unlikely AMI, according to criteria established by a panel of cardiologists. Only patients with diagnoses that met the criteria for definite or probable AMI were included in the study. A definite AMI included any one or all of the following: (1) positive findings at autopsy, (2) sequential electrocardiographic (ECG) changes typical of AMI, (3) history of chest pain typical of AMI, *with* enzyme elevation in the pattern expected of AMI, *and* ST depression ($\geq$ 1 mm) with T wave inversion and (4) shock with a history of enzyme or ST-T changes. A probable AMI included any of the following: (1) enzyme elevation and appearance of a new bundle branch block, (2) enzyme elevation in the pattern expected of AMI and ST depression ($\geq$1 mm) with T wave inversion and (3) shock or acute heart failure *without* another explanation.

Procedure

Before discharge from the CCU, each patient was informed that the hospital was participating in a heart disease study and that they would be mailed follow-up questionnaires for five years. At four months, a year, and yearly thereafter from the date of admission to CCU, each patient was sent a questionnaire with an explanatory letter. If the questionnaire was not returned within three weeks, a duplicate was mailed. Questionnaire data were punched on computer cards and transferred to tape.

Cause of Death

Notification of a patient's death was received from family, friends or obituaries, and the date, cause and location of each death was obtained. Cause of death was collected from autopsy reports when available, and from physicians, hospital records and death certificates. The causes of death were divided into three categories: (1) MI or AMI, (2) other (all other deaths with known causes not attributable to a reinfarction) and (3) unknown.

Classification

Patients were grouped according to symptoms reported during each year of follow-up. Questionnaires listed the symptoms commonly experienced following a myocardial infarction such as shortness of breath, swelling of ankles, waking up short of breath, chest pain, weakness and palpitations or pounding of the heart. Patients were classified according to the number of yes responses. (Waking up short of breath *and* shortness of breath were tabulated as a single yes response.) Group 1 contains patients with no symptoms, group 2 those with one to two symptoms, group 3 those with three to four symptoms and group 4 those with at least five symptoms.

Study Group

There were 2,020 patients admitted to CCU's and diagnosed as having had either a definite or probable AMI. Of these, 1,641 (81.4 percent) patients survived the acute (CCU) and convalescent periods (post-CCU) in hospital; 146 of these patients were not followed further because 75 (4.6 percent) did not receive their doctors' permission to participate and 71 (4.3 percent) did not respond to the questionnaires (Figure 1).

The follow-up group contained 1,495 patients (Figure 1). Of these patients, 124 (8.3 percent) died after hospital discharge but within four months of CCU admission and, therefore, before the mailing of the first follow-up questionnaire. Of the 2,020 patients who met the criteria for MI, 1,371 (67.9 percent) were known to be alive

four months after CCU admission and comprised the group available to respond to questionnaires. There was a male:female ratio of 3.5:1 (Figure 1).

There was a higher percentage of men in the younger age groups, and a higher percentage of women in the age group of 71 years and older than would be expected. Forty-six of the 48 patients (95.8 percent) who were younger than 40 years old were men. However, 212 (62.5 percent) of the 339 patients 71 years of age or older were men, in comparison with 127 (37.5 percent) women. This difference in the age-sex distribution of 1,371 patients eligible for follow-up was statistically significant (Mantel-Haenszel x^2 $P<0.001$).

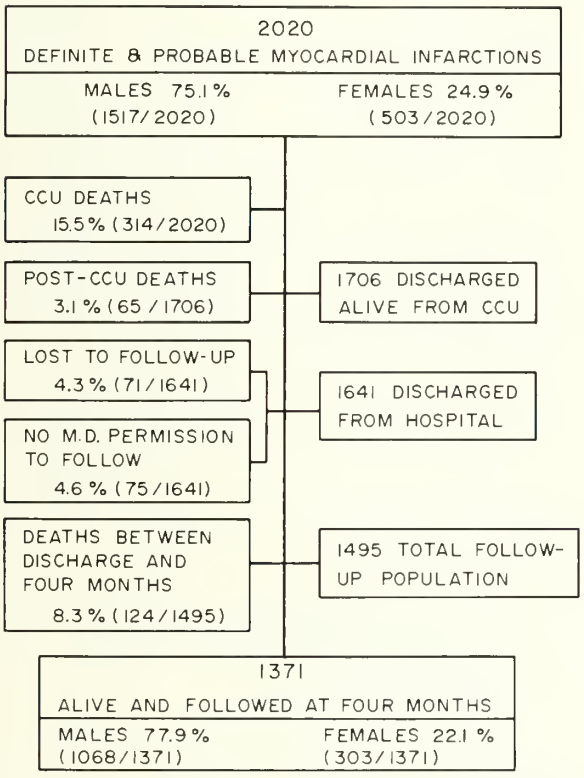


Figure 1.—Derivation of myocardial infarction patient population for follow-up statistics from 12 Utah hospitals, January 1970 through December 1972.

Similar differences have been reported by other authors (Table 1).

Results

Mortality

Of the 1,517 men in the study, 665 (43.8 percent) were dead at the end of the fifth year, as compared with 284 (56.5 percent) of the 503 women. The percentage of women who died was also greater in the CCU and post-CCU periods (Table 2). Of the 1,495 patients discharged and followed, 570 (38.1 percent) had died by the end of the fifth year. In all, 417 (36.0 percent) of the 1,157 men and 153 (45.3 percent) of the 338 women died during follow-up (Table 3).

The greatest number of follow-up deaths occurred immediately after discharge from hospital (Table 4). Of the 570 deaths during follow-up, 124 (21.75 percent) occurred within the first four months. Mortality was also high during the following eight months; 109 deaths occurred in this interval, representing 19.2 percent of the follow-up deaths. The yearly mortality during the remaining follow-up period was fairly consistent (Table 4).

A larger proportion of women in comparison to men were 71 years or older. Of the 153 women who died during follow-up, 127 (54.9 percent) were 71 years or older; 149 (35.7 percent) of the 417 men who died during follow-up were in this age group.

The 446 deaths which occurred from four

TABLE 2.—*Deaths of 379 Patients With Myocardial Infarction in Hospital*

	Males (N=1,517)	*Females (N=503)*	*Total (N=2,020)*
CCU deaths	208(13.7)	106(21.0)	314(15.5)
Post-CCU deaths ..	40(2.4)	25(5.0)	65(3.2)
Total hospital deaths	248(16.1)	131(26.0)	379(18.7)

MI = myocardial infarction; CCU = coronary care unit

*Percentages are given in parentheses.

TABLE 1.—*Age and Sex Distribution of Patients With Myocardial Infarction Four Months After Hospital Discharge*

	Age Group (Years)					
	<40	*41-50*	*51-60*	*61-70*	*>70*	*Total**
Males	46(95.8)†	186(90.3)	329(82.5)	295(77.8)	212(62.5)	1,068
Females ...	2(4.2)	20(9.7)	70(17.5)	84(22.2)	127(37.5)	303
TOTAL .	48	206	399	379	339	1,371

*These are known deaths for analysis; the 146 patients not followed have been omitted. (Mantel-Haenszel x^2 $P<0.001$).

†Percentages are given in parentheses.

months to five years after initial admission to CCU were compared on the basis of sex and age (Figure 2). Although a higher percentage of women were older in comparison to men, the percentage of deaths calculated from the number of patients within each group did not differ significantly (Mantel-Haenszel x^2 [corrected] $P = 0.697$).

Cause of Death

The major cause of death during the CCU and post-CCU periods was MI, accounting for 290 (76.5 percent) of the 379 deaths. The percentage of deaths attributable to reinfarction declined after the acute phase of illness (Table 5). Of the 124 deaths occurring between discharge and four months, 68 (54.8 percent) were due to MI; 164 (36.8 percent) of the 446 deaths from four months to five years of follow-up were also due to MI.

TABLE 3.—*Deaths of 570 Patients With Myocardial Infarction During Follow-up*

Occurrence of Deaths	*Males (N = 1,157)*	*Females (N = 338)*	*Total* (N = 1,495)*
Discharge to 4 months	89(7.7)†	35(10.3)	124(8.3)
4 months to 5 years	328(28.3)	118(35.0)	446(29.8)
Total during follow-up	417(36.0)	153(45.3)	570(38.1)

*These are *known* deaths, for analysis; the 146 patients not followed have been omitted.

†Percentages are given in parentheses.

TABLE 4.—*Distribution of Deaths of 570 Patients With Myocardial Infarction During Follow-up*

Time of Follow-Up	*No. of Deaths*	*Total % of Follow-Up Deaths*	*Yearly Mortality**
0-4 months	124	21.75	8.29
4 months-1 year	109	19.12	7.95
1-2 years	90	15.78	7.13
2-3 years	93	16.32	7.93
3-4 years	88	15.44	8.16
4-5 years	66	11.58	6.65
TOTAL	570		

*Based on 1,495 patients followed after hospital discharge.

Symptom Groups

Patients who survived through the fifth year of follow-up were grouped at years one and five according to the number of symptoms reported. There were 925 patients known to be alive at the end of year five. When comparing these patients according to symptoms reported at years one and five, there was no significant difference in symptom groups (Mantel-Haenszel x^2 $P = 0.146$, Figure 3).

Differences existed between those patients who were alive after five years of follow-up and those who died during follow-up with respect to symptoms experienced at year one (Figure 4). A greater number of patients alive at the fifth year of follow-up were in symptom groups 1 and 2 (zero or one to two symptoms reported) versus groups 3 and 4. Of the 925 patients alive at year five, 29.4 percent were in symptom group 1 and 34.7 percent in symptom group 2 at year one of follow-up. Of the 337 patients who died from year one through year five, 26.7 percent were in symptom group 1 and 25.5 percent in group 2 at year one

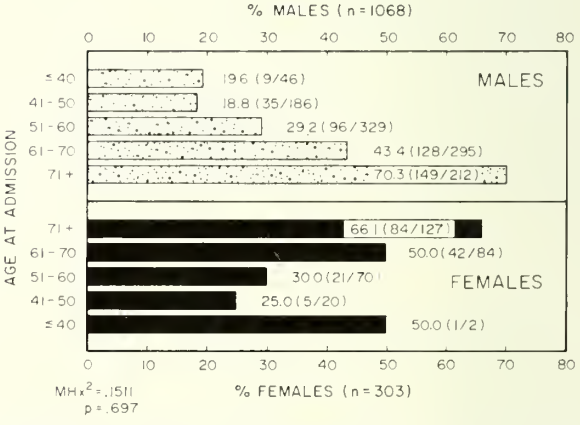


Figure 2.—Age and sex distribution of 446 patients with myocardial infarction who died between four months and five years after admission to coronary care units.

TABLE 5.—*Cause of Death for 949 Patients With Myocardial Infarction During Five-Year Follow-up*

Cause	*In Hospital*	*Deaths Between Discharge and 4 Months*	*Deaths Between 4 Months and 5 Years*	*Total*
Acute myocardial infarction	290(76.5)	68(54.8)	164(36.8)	522
All others	89(23.5)	39(30.6)	244(54.7)	371
Unknown	0	18(14.5)	38(8.5)	56
TOTAL	379	124	446	949

of follow-up. These differences were significant (Mantel-Haenszel x^2 $P = 0.0146$—patients not followed were not included in statistical analysis).

Patients alive at years one and five of follow-up did not differ in the number of symptoms reported on the questionnaire before death when compared with those patients who died during follow-up.

Patients who died from four months to five years after admission to CCU with a diagnosis of MI were grouped at year one after CCU admission. No correlation was found between the symptom group and the amount of time that had elapsed until death. Patients reporting no symptoms at year one survived a mean of 32.1 months, while patients reporting three or four symptoms survived a mean of 31.4 months.

Cause of Death and Symptom Group

Fifty-four (32.9 percent) patients who died of another infarction after four months to five years of follow-up were in symptom group 1—reporting no symptoms on the questionnaire before death. Approximately half (48.1 percent) had reported one to four symptoms and 20 (12.2 percent) patients of the 164 who died of MI during follow-up had reported five symptoms. Cardiac symptoms reported before death, as measured in this study, are apparently of no predictive value in determination of the ultimate cause of death. Patients reporting a higher number of cardiac-related symptoms did not necessarily die of another infarction.

Discussion

Patient participation in follow-up was voluntary and the response was excellent. After five years of follow-up, 925 of the 2,020 patients who had been admitted to hospital with a definite or probable MI were known to be alive (45.8 percent). The status of the 146 patients not followed was unknown at year five. In comparison to studies by other authors, this figure falls midway in the percentage of survivors reported.[11-18] Differences in sex, age and associated diseases in patients among various studies make comparisons difficult. The most closely related study is that of Goldberg and co-workers,[19] who reported five-year survival rates during two investigations. The first (1969 to 1971) reported a 73.4 percent five-year survival and the second (1971 to 1973) a 69.5 percent five-year survival. The higher mortality in our study is probably a reflection of the fact that all hospital admissions were followed and not only first infarctions.

As reported in other investigations,[14,15] our data show a difference in mortality between men and women patients with MI. Women showed a higher death rate during CCU, post-CCU and follow-up. Women were also older when they had an MI[20,21] and a greater proportion of females were in the higher age groups than expected (Table 1). Although 66.1 percent of the women 71 years of age or older died during follow-up, a higher percentage of men in this age group died (70.3 percent). These results indicate, as reported elsewhere, that mortality after MI increases with age.[1,3,6,22] As indicated in our study, when male and female patients were matched according to age, mortality differences diminished. Librach and co-workers,[22] reporting on relative mortality for men and women MI patients over 65 years of age, found a higher mortality for men, which was also indicated in our

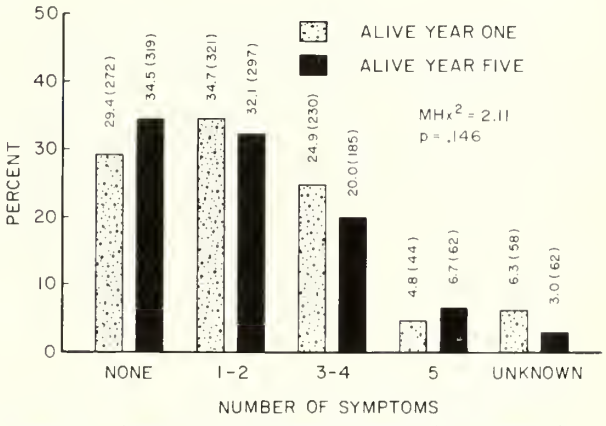


Figure 3.—Distribution of 925 patients with myocardial infarction according to number of symptoms at years one and five of follow-up.

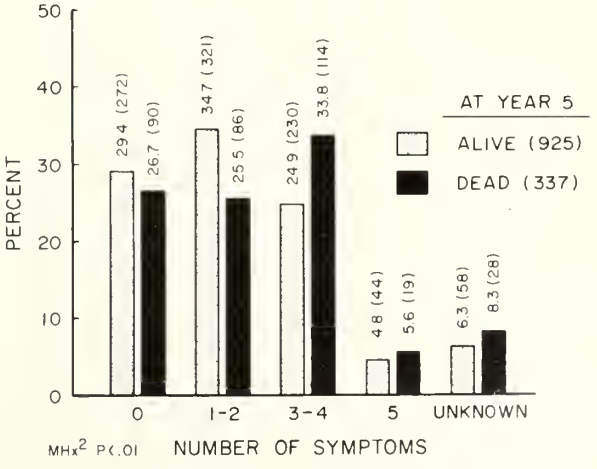


Figure 4.—Comparison of symptom groups at year one for patients alive and dead at year five of follow-up.

study. Other studies also have a higher percentage of men in their study group. The Göteborg, Sweden, investigation by Vedin and colleagues[23] reported that healthy women showed an overall lower incidence of initial infarction than men, but once experiencing an MI, the subsequent mortality from reinfarction was not lower for women.[23] According to these data, it appears that while a lower percentage of women experience MI's, once they have suffered an infarction, their chance of reinfarction or of long-term survival does not differ and may be even worse than that of men.

Cause of Death

When the data were analyzed for cause of death, it was found that 164 (36.8 percent) of the 446 deaths occurring during follow-up were due to MI. Myocardial infarction was diagnosed as the cause of 34 percent of the follow-up deaths in a study by Juergens and co-workers,[20] while Kannel and colleagues[14] reported 34.5 percent of follow-up deaths attributable to MI. We found that a lower percent of follow-up deaths in women was the result of MI's: 33 (27.7 percent) of the deaths among women and 131 (39.9 percent) of the deaths among men were listed as MI's. While women showed an overall higher mortality during follow-up, the relative percentage of deaths among women attributable to subsequent infarction is lower than the percentage of men who died of recurrent infarction.

Symptom Groups

An attempt was made to see if correlations existed between the number of cardiac symptoms reported by patients after MI and their subsequent outcome during five years of follow-up. Few differences were noted in comparing patient responses at year one and year five. When patients were grouped at year one according to the number of reported symptoms, some differences did exist between patients who survived the follow-up period and those who died (Figure 4). A higher percentage of patients who survived five years had reported on the first year questionnaire zero through two symptoms in comparison to patients who had died during follow-up.

On the last questionnaire before death, the 446 patients who had died during follow-up did not report a greater number of symptoms in comparison to patients alive at years one and five. Of the patients who died, 135 (30.3 percent) had reported no cardiac-related symptoms; however, it is possible that patients tended to minimize or deny symptoms. Because questionnaires were mailed at yearly intervals, an increase in the number of cardiac symptoms before death was possibly not reported due to the inability of a yearly questionnaire to detect such changes. On the basis of this information it appears that an increase of symptoms might not be observed before death in many patients. While a difference in the number of symptoms reported at year one of the follow-up was found between patients alive and dead at five years, it is not possible to predict on the basis of symptom group which patients will die during a five-year follow-up period.

REFERENCES

1. Richard DW, Bland EF, White PD: A completed 25-year follow-up of 200 patients with MI. J Chron Dis 4:415-422, 1956

2. Katz LN, Mills GY, Cisneros F: Survival after recent myocardial infarction. Arch Intern Med 84:305-318, 1949

3. Cole DR, Singian EB, Katz LN: The long-term prognosis following myocardial infarction and some factors which affect it. Circulation 9:321-334, 1954

4. Day HW: Effectiveness of an intensive care unit. Am J Card 15:51-54, 1965

5. Goble AJ, Sloman G, Robinson JS: Mortality reduction in a coronary care unit. Br Med J 12:1005, 1966

6. Hofvendahl S: Influence of treatment in a coronary care unit on prognosis in acute myocardial infarction: A controlled study in 271 cases. Acta Med Scand (Suppl) 519:9-78, 1971

7. Helmers C: Short and long-term prognostic indices in acute myocardial infarction—A study of 606 patients initially treated in a coronary care unit. Acta Med Scand (Suppl) 555:7-26, 1973

8. Norris RM, Caughery DE, Mercer CJ, et al: Prognosis after myocardial infarction: Six year follow-up. Br Heart J 36:786-790, 1974

9. Peel AAF, Semple T, Wang I, et al: A coronary prognostic index for grading the severity of infarction. Br Heart J 24:745-760, 1962

10. Pell S, O'Alonzo CA: Immediate mortality and five-year survival of employed men with a first myocardial infarction. N Engl J Med 270:915-922, 1964

11. Mulcahy R, Hickey N, Graham IM, et al: Factors affecting the 5-year survival rate of men following acute coronary heart disease. Am Heart J 93:556-559, 1977

12. Karwatowska-Krynska E, Ceremuzynski L: A five-year follow-up study of 235 male patients discharged from hospital after acute myocardial infarction. Materia Medica Polona 3(32):252-255, 1977

13. Sigler LH: Long-term survival following myocardial infarction: Report of 255 patients living ten years or longer after the first attack. Am J Cardiol 9:947, 1962

14. Kannel WB, Sorlie P, McNamara PM: Prognosis after initial myocardial infarction: The Framingham study. Am J Cardiol 44:53-59, 1979

15. Geismar P, Iversen E, Mosbech J, et al: Long-term survival after myocardial infarction: A national follow-up study on 642 patients in Denmark. Int J Epid 2:257-263, 1973

16. Kitchin H, Pocock SJ: Prognosis of patients with acute myocardial infarction admitted to a coronary care unit. Br Heart J 39:1167-1171, 1977

17. Helmers C, Lundman T: Early and sudden deaths after myocardial infarction. Acta Med Scand 205(1-3):3-9, 1979

18. Helmers C, Lundman T, Maasing R, et al: Mortality pattern among initial survivors of acute myocardial infarction using a life-table technique. Acta Med Scand 200:469-473, 1976

19. Goldberg R, Szklo M, Tonasca JA, et al: Time trends in prognosis of patients with myocardial infarction. Johns Hopkins Med J 144:73-80, 1979

20. Juergens JL, Edwards JE, Achor RWP, et al: Prognosis of patients surviving first clinically diagnosed myocardial infarction. Arch Intern Med 105:444-450, 1960

21. Sievers J: Myocardial infarction clinical features and outcome in 3036 cases. Acta Med Scand (Suppl) 406:1-123, 1963

22. Librach G, Schadel M, Seltzer M, et al: Immediate and long-term prognosis of acute myocardial infarction in the aged. J Chron Dis 29:483-495, 1976

23. Vedin A, Wihelmsson C, Elmfeldt D, et al: Deaths and non-fatal reinfarctions during two years follow-up after myocardial infarction. Acta Med Scand 198:353-364, 1975

Refer to: Geffner ME, Powars DR, Choctaw WT: Acquired methemoglobinemia. West J Med 134:7-10, Jan 1981

Acquired Methemoglobinemia

MITCHELL E. GEFFNER, MD; DARLEEN R. POWARS, MD, *and*
WILLIAM T. CHOCTAW, MD, *Los Angeles*

Cases of acquired methemoglobinemia have been identified with increasing frequency in Los Angeles during the last several years. Among 18 patients, both infants and adults, the most commonly incriminated agent was silver nitrate used for topical antibacterial prophylaxis of burn wounds. One burned child died from overwhelming septicemia complicated by hypoxia with a methemoglobin level of 5.4 grams per dl. Other causative factors included nitrate-rich vegetables used in early infancy, additives in ethnic foods, and prescribed and overdosed drugs. Discontinuation of the precipitating agent and methylene blue therapy were usually followed by prompt improvement. In burned patients treated with silver nitrate, careful regular monitoring of serum methemoglobin levels and early initiation of specific therapy are mandatory.

THAT METHEMOGLOBINEMIA may complicate nitrate or nitrite use in infants, children and adults has been well recognized for many years. Recently, we have observed an upsurge in the incidence of this complication in four specific areas: (1) application of topical silver nitrate in the treatment of burns; (2) introduction of vegetables with high nitrate content into the diets of infants younger than 3 months of age; (3) ingestion of additives in ethnic foods among populations from Mexico, Southeast Asia and the Philippines, and (4) use of certain prescribed drugs.

We wish to report on our experience of patients with acquired methemoglobinema in a metropolitan hospital in central-city Los Angeles between 1973 and 1978. Recently, excellent reviews of methemoglobinemia, including unresolved issues of biochemistry, have been published.[1,2]

From the Department of Pediatrics (Drs. Geffner and Powars), and the Burn Center, Department of Surgery (Dr. Choctaw), University of Southern California School of Medicine, Los Angeles. Dr. Geffner is now Fellow, Division of Pediatric Endocrinology, University of California, Los Angeles, Center for the Health Sciences.

Submitted, revised, August 1, 1980.

Reprint requests to: Darleen R. Powars, MD, LAC-USC Medical Center, 1129 North State Street, Los Angeles, CA 90033.

Patients, Methods and Results

All patients with known methemoglobinemia between 1973 and 1978 were evaluated. Abnormal levels of methemoglobin were considered those above 0.2 grams per dl. Methemoglobin levels were determined by the Gilford-240 spectrophotometer (Overland, Ohio), which clearly distinguishes methemoglobin from sulfhemoglobin. Table 1 includes the ages of patients, dates of diagnoses, maximum methemoglobin levels, methemoglobin levels expressed as a percent of the total hemoglobin concentration, offending agents if known and treatment modalities used. Of the 18 patients identified, 4 were younger than 1 year of age, 2 were between 1 and 18 years old and 12 were adults.

Our hospital is a major referral center for

moderately to severely burned patients. Topical silver nitrate (via continuous drip) has been the mainstay in the prevention of secondary infection in such patients; consequently, at present it is the most common identifiable cause of acquired methemoglobinemia (7 of 18 cases). Nitrate-containing prescription drugs (4 of 18), accidental overdosages (2 of 18), food additives (2 of 18) and nitrate-rich vegetables in early infancy (2 of 18) constitute the remaining causes. In only one case could no cause whatsoever be ascertained. During this six-year study period, there were no known cases of methemoglobinemia associated with exposure to aniline dyes, well water or vitamin K analogues. Table 2 lists the incriminated agents and the number of cases involved.

At our burn center we maintain a high index of suspicion for methemoglobinemia in patients who are receiving topical silver nitrate antibacterial prophylaxis. However, the identification of an altered skin appearance (that is, cyanosis) for diagnosis poses severe clinical difficulties of recognition in burned patients in view of pronounced skin disruption, dressings applied over a substantial amount of surface area, skin color changes induced by the silver nitrate itself and, often, precarious cardiovascular status. Clinical diagnosis must therefore be based primarily on the observation of dark "chocolate-colored" blood obtained during the frequent phlebotomies of these patients. In the remainder of our sample population, either clinical cyanosis was the presenting problem or methemoglobinemia was a fortuitous laboratory finding. Methemoglobin reductase levels were measured in selected patients, including a husband and wife who ingested sodium nitrate and several infants who ate nitrate-rich vegetables. Reductase levels were determined to be normal for age. Burned patients who had received multiple prior transfusions were not tested.

Discussion

In general, the cause of methemoglobinemia in adult patients relates to drugs, industrial exposures, cultural dietary patterns and recreational use of nitrates.[3] The infant group is at risk from the ingestion of vegetables rich in nitrates such as spinach, beets, carrots, turnips and cabbage, as well as from well water, skin contact with medicines and chemicals, and accidental ingestions.[1,4]

Several of our children were given spinach and other vegetables during the first three months of life. Of note is that bottles of Gerber baby spinach

TABLE 1.—*Case Descriptions of 18 Patients With Acquired Methemoglobinemia*

Case Number	*Age*	*Date of Diagnosis*	*Maximum Methgb. Level (grams per dl)*	*Methgb. Level as Percent of Total Hemoglobin*	*Cause*	*Treatment*
1	1 mo	1/19/74	1.1	10	Unknown	None
2	51 yr	10/28/74	0.3		Nitroglycerin	Discontinue drug
3	21 yr	5/11/75	2.3	28	$AgNO_3$ for burn	Change to sulfadiazine
4	26 yr	8/15/75	0.5		Chloroquine	Discontinue drug
5* ...	29 yr	6/ 3/76	9.1	70	Sodium nitrate salt (food additive)	Methylene blue
6* ...	27 yr	6/ 3/76	3.0	30	Sodium nitrate	Methylene blue
7	43 yr	8/ 8/76	3.0	30	$AgNO_3$ for burn	Methylene blue, change to sulfadiazine
8	56 yr	8/28/76	0.4		Isosorbide dinitrate	Discontinue drug
9	3 yr	9/20/76	0.3		$AgNO_3$ for burn	Methylene blue, discontinue $AgNO_3$
10	33 yr	10/ 6/76	0.3		$AgNO_3$ for burn	Discontinue $AgNO_3$
11	36 yr	4/16/77	1.9	13	Deodorant containing butyl nitrite	Discontinue agent
12	82 yr	6/10/77	0.3		$AgNO_3$ for burn	Discontinue $AgNO_3$
13	44 yr	7/14/77	0.4	4	$AgNO_3$ for burn	Discontinue $AgNO_3$
14	1 mo	10/ 9/77			Spinach water	Methylene blue
15	27 yr	2/19/78	0.3	3	Tricofuron†	Discontinue agent
16	17 mo	11/16/78	0.4	3	Phenazopyridine	Discontinue agent
17	6 wks	11/26/78	2.8	35	Gerber pureed spinach, beets and carrots	Methylene blue
18	3 mo	12/28/78	5.4	45	$AgNO_3$ for burn	Methylene blue

$AgNO_3$ = silver nitrate; Methgb = methemoglobinemia

*Married Filipino couple.

†This formerly available product contains furizolidone and nifuroxamine (both of which contain nitrate groups) and was used intravaginally for the treatment of trichomoniasis.

TABLE 2.—*Causes of Acquired Methemoglobinemia*

Cause	*Number of Cases*
Silver nitrate	7
Prescribed drugs	4
Overdosages of drugs	2
High-nitrate vegetables ingested during early infancy	2
Food additives	2
Unknown	1
TOTAL	18

recommend—albeit in very small print—that this product is not to be given to infants younger than 12 weeks of age. Additionally, the American Academy of Pediatrics clearly recommends avoidance of spinach and other nitrate-rich vegetables in their recent report on infant feeding.[5] Nitrates as preservatives are usually found in highest concentrations in foods not ordinarily eaten by younger children, such as hot dogs, bacon, ham, lunch meats and some imported cheeses.[6]

In susceptible infants, as well as adults, the intake of nitrate-rich vegetables may be harmful if the nitrate is converted to hazardous nitrite. This may occur by either of two mechanisms: contamination by bacteria capable of nitrate reduction during processing or chemical reduction as a result of the plant's intrinsic enzymes.[7] Furthermore, infants during the first few months of life are known to have a lower gastric acidity with a resultant proliferation of bacterial species capable of reducing nitrate to nitrite.[8] This latter factor combined with the known low physiological levels of protective erythrocyte methemoglobin reductase predisposes the infant population to a risk greater than among older persons.[9] Normal erythrocytic methemoglobin reductase is capable of reducing methemoglobin at 250 times the physiological rate of formation.[10] Only when the toxic agent has saturated this protective mechanism does methemoglobin accumulate in erythrocytes. Methemoglobin changes the cooperativity of the hemoglobin molecule resulting in a shift of the oxygen dissociation curve to the left, thereby decreasing delivery of oxygen to the tissues.[11,12]

In mild degree, dietary-induced methemoglobinemia is of minimal clinical significance. If methemoglobin levels remain below 1 gram per dl, most patients are asymptomatic. When clinically indicated, methylene blue (1 to 2 mg per kg of body weight) or ascorbic acid (200 to 500 mg per day) is effective therapy. It should be noted that in patients who are deficient in glucose-6-phosphate dehydrogenase (G-6PD), administration of methylene blue has been reported to cause a Heinz-body hemolytic anemia.[13] We have, in addition, observed the development of a severe Heinz-body hemolytic anemia in an infant with normal values for G-6PD who was accidentally administered an excessive dose of methylene blue (10 mg per kg of body weight).

The as yet unsolved problem posed by large areas of second and third degree burns and the appropriate prophylaxis of secondary bacterial infections is of major concern in our burn center. Silver nitrate, silver sulfadiazine and combinations of them are the best and safest agents for the prophylaxis of burn wound infections.[14] Most deaths among burned patients of all ages result from the problem of severe, overwhelming infection. Acquired methemoglobinemia in our burned patients had three prerequisites (1) a source of nitrate (silver nitrate), (2) a mechanism of nitrate reduction (the proliferation of microorganisms capable of reducing nitrate to nitrite (such as *Pseudomonas aeruginosa, Enterobacter* species, *Escherichia coli, Serratia marcescans,* and some *Proteus* species)[15] and (3) an altered barrier through which the nitrite can be absorbed into the bloodstream (the surface area of burned skin).[16]

It is the goal of topical antibiotic drugs to prevent any infection of the wound. Initiation of methylene blue therapy in patients with complicated burns must be individualized to the clinical status of each patient. The physicians at our burn center have observed tachypnea, tachycardia and other signs of hypoxia which were immediately improved following methylene blue therapy in patients with methemoglobin levels of less than 1 gram per dl (case 9). In the event that methemoglobin levels increase beyond the safe range, but no related symptomatology is seen, discontinuing application of silver nitrate for two or three days is effective. In addition, substitution of alternative topical antisepsis, such as mafenide acetate or silver sulfadiazine, should be made. It should be cautioned, however, that clinical methemoglobinemia, or more likely, sulfhemoglobinemia, has recently been reported in two 2-year-old children treated with mafenide acetate for 50 percent surface burns.[17] Although sulfhemoglobinemia differs clinically from methemoglobinemia by the gross mauve-lavender color imparted to the blood, its irreversibility and its production of cyanosis at

lower concentrations, the two can be precisely differentiated by readily available spectrophotometric equipment.[18]

Of special note is one severely burned 3-month-old infant (case 18) treated with silver nitrate in whom methemoglobin levels reached 5.4 grams per dl (4 percent). The infant died three days after the burns were incurred. Findings at autopsy showed second and third degree burns over 75 percent of the child's body, septicemia, disseminated intravascular coagulation and diffuse manifestations of hypoxia. Two other children have been reported in the literature, aged 3 and 5 years in whom complications of methemoglobinemia developed after 15 and 26 days of therapy with silver nitrate, and who died on hospital days 27 and 30, respectively.[16,19] Both were colonized with nitrate-reducing bacteria.[15] Methemoglobinemia had developed in our infant on only the third hospital day and she died within 24 hours. Although the child's prognosis was grim by virtue of the extent of the burns and their complications, severely compromised oxygen transport may have contributed to her death. The case of this extremely ill, septic and burned infant clearly illustrates the problems encountered with methemoglobin toxicity.

Conclusion

We recommend that burn centers using silver nitrate antisepsis regularly monitor methemoglobin levels in their patients. A prospective study is needed to provide data regarding the true incidence of methemoglobinemia and the resultant clinical consequences on these severely burned patients.

REFERENCES

1. Herzog P, Feig SA: Methaemoglobinaemia in the newborn infant. Clin Haematol 7:75-83, 1978

2. Committee on Nutrition: Infant methemoglobinemia: The role of dietary nitrate. Pediatrics 46:475-477, 1970

3. Hamblin DO: Aromatic nitro and amino compounds, chap 47, *In* Patty FA (Ed): Industrial Hygiene and Toxicology, Vol II, 2nd Ed. New York, Interscience Publishers, 1963

4. Keating JP, Lell ME, Strauss AW, et al: Infantile methemoglobinemia caused by carrot juice. N Engl J Med 288:824-826, 1973

5. Committee on Nutrition: On the feeding of supplemented foods to infants. Pediatrics 65:1178-1181, 1980

6. Magee PN: Toxicity of nitrosamines: Their possible human health hazards. Food Cosmet Toxicol 9:207-218, 1971

7. Paneque A, Del Campo FF, Ramirez JM, et al: Flavin nucleotide reductase from spinach. Biochem Biophys Acta 109: 79-85, 1965

8. Nitrates and nitrites in food. Med Lett Drugs Ther 16:75-76, 1974

9. Bartos HR, Desforges JF: Erythrocyte DPNH dependent diaphorase levels in infants. Pediatrics 37:991-993, Jun 1966

10. Scott EM: Congenital methemoglobinemia due to DPNH diaphorase deficiency, *In* Beutler E (Ed): Hereditary Disorders of Erythrocyte Metabolism. New York, Grune and Stratton, 1968, pp 102-113

11. Enoki Y, Tokui H, Tyuma I: Oxygen equilibrium of partially oxidized hemoglobin. Respir Physiol 7:300-309, 1969

12. Smith RP, Olson MV: Drug-induced methemoglobinemia. Semin Hematol 10:253-268, 1973

13. Coluboff N, Wheaton R: Methylene blue induced cyanosis and acute hemolytic anemia complicating the treatment of methemoglobinemia. J Pediatr 58:86-89, 1961

14. Monafee WM: An overview of infection control. J Trauma 19:879-880, 1979

15. Skerman VBD: A Guide to the Identification of the Genuses of Bacteria. Baltimore, Williams & Wilkins Co, 1959, pp 61, 89-96

16. Ternberg JL, Luce E: Methemoglobinemia: A complication of the silver nitrate treatment of burns. Surgery 63:328-330, 1968

17. Ohlgisser M, Adler M, Ben-Dov D, et al: Methaemoglobinaemia induced by mafenide acetate in children. Br J Anaesth 50: 299-301, 1978

18. Wintrobe MM, Lee GP, Boggs DR, et al: Methemoglobinemia and other disorders usually accompanied by cyanosis, *In* Wintrobe MM (Ed): Clinical Hematology, 6th Ed. Philadelphia, Lea and Febiger, 1974, pp 1009-1020

19. Cushing AH, Smith S: Methemoglobinemia with silver nitrate therapy of a burn: Report of a case. J Pediatr 74:613-615, 1969

Refer to: Mahal AS, Knauer CM, Gregory PB: Bleeding after liver biopsy. West J Med 134:11-14, Jan 1981

Bleeding After Liver Biopsy

ANMOL S. MAHAL, MD; C. MICHAEL KNAUER, MD, *and*
PETER B. GREGORY, MD, *Stanford, California*

During nine years 3,080 liver biopsies were carried out and bleeding occurred in 22 of the patients (0.7 percent). Transfusions were given to 17 of these patients and laparotomies were done to control the bleeding in six. All survived. Bleeding was evident within three hours in 19 patients, but occurred from 3 to 13 days after biopsy in the remaining three. Pain requiring analgesic medication and a fall in blood pressure were the usual indications that major bleeding had occurred. Relative contraindications to biopsy (particularly a prolonged prothrombin time) were present in 10 of the 22 bleeding patients and in only 2 of the 41 nonbleeding controls ($P<0.001$). We believe that some of the bleeding episodes could have been prevented with more careful attention to the indications and contraindications to biopsy, and more rigorous correction of recognized clotting abnormalities.

PERCUTANEOUS LIVER BIOPSY is used widely for the diagnosis, staging and follow-up of hepatic disease. Complications of this procedure include pain, bleeding, pneumothorax, bile peritonitis, arteriovenous fistula formation, intrahepatic hematomas, bacteremia and inadvertently taking specimens from other organs.[1-7] Of the serious complications, bleeding is the most common, with an incidence ranging from 0.8 percent to 1 percent.[1,5,6] Subsequent fatality may occur in as many as 3 out of 10,000 biopsies.[6]

In this report, we describe our experience with postbiopsy bleeding in 22 patients and provide a partial explanation for its occurrence.

Patients and Methods

A total of 3,080 percutaneous liver biopsies were carried out in adult patients at the Stanford University Medical Center, the Santa Clara Valley Medical Center and the Veterans Administration Medical Center from January 1970 through December 1978. In all patients, evaluations were done by the gastroenterology consultation team or their private physicians before biopsy. Most biopsies were done either by the medical resident or gastroenterology fellow; 18 percent were done by physicians in private practice.

The biopsies were done by the suction aspiration technique using a modified Menghini (Klatskin) needle.[8] The approach was transthoracic with the patient lying on his back and holding his breath. The point of entry was between the midaxillary and posterior axillary line. After biopsy the patient was advised to lie on his right side for two hours and remain in bed overnight. A total of 171 patients who had liver biopsies done as outpatients were allowed to leave six hours after the procedures and advised to rest at home.

Contraindications to liver biopsy during the study period were a prothrombin time less than 50 percent, partial thromboplastin time greater

From the Departments of Medicine, Stanford University School of Medicine, Stanford, California; Santa Clara Valley Medical Center, San Jose, California, and Veterans Administration Medical Center, Palo Alto, California.
Sponsored in part by research grant No. 76273 from the John A. Hartford Foundation, Inc.
Submitted June 13, 1980.
Reprint requests to: Peter B. Gregory, MD, SO69, Department of Medicine, Stanford University School of Medicine, Stanford, CA 94305.

than 10 seconds over control, a platelet count less than 50,000 or an abnormal bleeding time.

There were 22 patients who bled following liver biopsy (suspected on clinical grounds and confirmed by a drop in hematocrit of 5 hematocrit points or greater). The charts of these patients were reviewed in detail. For purposes of comparison we randomly selected the cases of 44 patients from the remaining 3,036 patients. The charts of 41 were available for review.

The data were analyzed by the two sample Student T test for continuous data or by the chi-square test for categorical data. Yates' correction for continuity was used in calculating the chi-square statistic when the expected frequencies were less than 5.[9]

TABLE 1.—*Age, Sex, Hematocrit, Indications for Biopsy and Histologic Diagnoses*

	Bleeding Group (22)	*Control Group (41)*
Age	46±3	46±2
Sex (male/female)	14/8	23/18
Hematocrit (percent)	34±2	37±1
Indications for biopsy		
Alcoholic liver disease	5	11
Acute hepatitis	6	5
Chronic hepatitis	3	2
Other*	8	23
Histologic diagnoses		
Acute viral hepatitis	2	2
Chronic persistent hepatitis	2	2
Chronic active hepatitis	2	2
Cirrhosis and chronic active hepatitis	0	1
Alcoholic hepatitis	5	2
Alcoholic cirrhosis	0	6
Alcoholic cirrhosis and hepatoma	1	0
Metastatic cancer	0	3
Lymphoma	1	2
Granulomatous hepatitis	3	0
Cholestatic hepatitis	1	3
Minor abnormalities (triaditis, congestion, fat, extramedullary hematopoiesis)†	2	13
Normal†	2	5
No liver tissue	1	0

*Includes biopsy for abnormal liver function tests, hepatomegaly, lymphoma staging, possible methotrexate toxicity and so forth.

†The observed difference between bleeding and control groups for those with minor abnormalities or a normal liver is significant at $P<0.05$.

TABLE 2.—*Treatment for Bleeding After Biopsy*

	Number of Patients	*Units of Blood**
Intravenous fluids	5	0
Transfusions	11	3±0.3
Transfusions and laparotomy	6	12±3

*Given as mean±1 S.E.M.

Results

Incidence of Bleeding, Patient Characteristics, Treatment and Outcome

In all, 3,080 percutaneous liver biopsies were carried out at our three hospitals during nine years. Twenty-two patients (0.7 percent) bled following biopsy. Table 1 gives the age, sex, pre-biopsy hematocrit, indications for biopsy, and histologic diagnoses in the bleeding patients and the control group. Bleeding patients were less likely than those in the control group to have normal liver tissue or minor histologic abnormalities ($P<0.05$). In other respects, the groups were comparable.

Treatment given to the 22 patients who bled is shown in Table 2. The five patients in whom no transfusions were needed had a mean hematocrit drop of 9 hematocrit points. In 11 patients transfusions were required to maintain vital signs, but their bleeding stopped spontaneously. In one patient in this group it was necessary to place a chest tube to drain a bloody right pleural effusion. Six patients continued to bleed and went to laparotomy after receiving an average of 12 units of blood (range 5 to 21 units). The findings were a hepatic artery to gall bladder fistula in one patient, a pinpoint puncture wound in two patients and lacerations of the right lobe of the liver in three patients. Five patients had at least 1,500 ml of blood in the peritoneal cavity and three had large intrahepatic hematomas that required draining. Surgical operations were not always simple, requiring two or more hours in four patients. Post-operative recovery was uneventful. All patients survived and were later discharged from hospital.

Initial Indications of Bleeding

Changes in vital signs and right upper quadrant pain requiring analgesia were the usual indications that a major hemorrhage had occurred (Table 3). The most common finding was a simultaneous drop in blood pressure and rise in pulse rate. In seven patients hypotension developed without a compensatory rise in pulse. Tachycardia without hypertension developed in one patient in both the bleeding and control groups. Vital sign changes were apparent within three hours in 19 patients who bled soon after biopsy. One of these patients stopped bleeding within 24 hours only to bleed again four days later. Three patients had stable hematocrits following biopsy, but then bled from 3 to 13 days later. Two of these three patients had

significant right upper quadrant pain immediately after the biopsy, but it subsided within six hours. Two of the four patients with delayed episodes of bleeding had hematobilia.

Pain requiring analgesia was noted immediately following biopsy in 12 bleeding patients and in only 5 control patients ($P<0.001$). All 12 patients had pain in the right upper quadrant or epigastrium. Four had pain in the right shoulder and three had pleuritic pain as well.

Examination at the time of bleeding found moderate to pronounced right upper quadrant tenderness in 17 of the 22 patients. Rebound tenderness was found in seven patients, and in six of these laparotomy was eventually required.

Etiologic Factors

Relative contraindications to liver biopsy are shown in Table 4. Ten patients in the bleeding group (45 percent) had one or more relative contraindications to liver biopsy whereas only two patients in the control group (5 percent) had any such abnormalities ($P<0.001$). In the bleeding group, seven patients had a single contraindication to biopsy and three had several. The prothrombin time identified six of these patients and was the only discriminating test ($P<0.003$).

The responsible physician chose to do the biopsy despite the contraindications to the procedure for varying reasons. In three patients the prothrombin time was in the 40 percent to 50 percent range. It was believed that the benefits of obtaining the histologic diagnosis outweighed the potential risk with this modest reduction in prothrombin time. Fresh frozen plasma was given to three other patients whose prothrombin times ranged from 30 percent to 40 percent. It rose to 59 percent in one patient, but no follow-up was done in the other two. An isolated prolongation of the partial thromboplastin time in one patient was not given serious consideration because a liver biopsy done five months previously had been uneventful. Although one patient had bled after a previous liver biopsy, the second procedure was undertaken when all her coagulation studies were found to be normal. Another patient, who had bled following delivery of her last baby, did not report this history until after the biopsy was done. The patient with a platelet count of less than 50,000 per cu mm received platelet transfusions but she bled nonetheless. None of the control patients received fresh frozen plasma or platelets.

One pass with the biopsy needle was made in 20 of the 22 bleeding patients and 38 of the 41 control patients. Two passes were made in one bleeding patient and three control patients. Three passes were made in one patient who bled. Liver biopsies were done by both experienced (fellows, faculty and practicing physicians) and relatively inexperienced (medical residents) operators. Bleeding was not more frequent in inexperienced hands.

The indications for biopsy in the ten bleeding patients who had one or more contraindications to biopsy were alcoholic liver disease (two patients), chronic hepatitis (four patients), acute viral hepatitis (one patient), lymphoma staging (one patient) and unexplained hepatomegaly (two patients).

Review of the hepatic histology did not show any large hepatic arteries in the biopsy specimens from those who bled.

Discussion

Major bleeding followed percutaneous liver biopsy in one of every 140 patients (0.7 percent).

TABLE 3.—*Initial Indications of Bleeding**

	Bleeding (22)	*Control (41)*
Fall in mean arterial pressure	7	0
Rise in pulse rate	1	1
Simultaneous change in blood pressure and pulse	14	0
Right upper quadrant pain requiring narcotic analgesia	12	5

*Differences between bleeding and control groups with respect to fall in mean arterial pressure, simultaneous change in blood pressure and pulse and right upper quadrant pain are all significant at $P<0.001$.

TABLE 4.—*Relative Contraindications to Liver Biopsy*

	Bleeding (22)	*Control (41)*
Prothrombin time <50 percent*	4	0
PTT >10 seconds over control	1	1
Platelets <50,000 per cu mm	1	0
Past history of bleeding	1	0
Abnormal bleeding time	0	1
Prothrombin time <50 percent and PTT >10 seconds over control*	2	0
Past history of bleeding and PTT >10 seconds over control	1	0
TOTAL†	10	2

PTT—partial thromboplastin time

*The difference between the bleeding and control patients in the number with a prothrombin time <50 percent is significant at $P<0.003$.

†The difference between the bleeding and control patients in the number with one or more contraindications to biopsy is significant at $P<0.001$.

This rate is higher than the 0.08 percent to 0.2 percent reported previously in two large surveys.[2,6] We believe that these surveys may have underestimated the true incidence of this complication. Our figures are drawn from three closely allied hospitals where we kept records of most liver biopsies performed and noted any subsequent complications. Had we not done this, it is likely we would have been unaware of the five patients in whom transfusions were not needed, and may have missed some of those in whom transfusions were required. It would not be unreasonable to suspect that similar cases were missed in the previous reports. If so, most published rates may be artificially low and the true rate closer to ours. Two small series do report an incidence of hemorrhage approximating our (0.4 percent and 0.9 percent)[10,11] and Perrault and co-workers in a series of 1,000 patients report a rate of 0.5.[12]

Bleeding occurs sufficiently frequently to warrant concern and a search for possible causes. We use a 16-gauge needle which has an external diameter of 1.6 mm. This is larger than the 1.2-mm caliber of the standard Menghini needle and produces (in our opinion) a better specimen. Others have claimed, however, that the risk of the procedure increases geometrically with the diameter of the needle.[2,8,13] A diameter of 2 mm or more appears particularly dangerous and a diameter of 0.7 mm carries very little risk.[2,14] Whether the 1.6-mm needle is more dangerous than the 1.2-mm needle remains to be shown. The possibility exists, however, that we have incurred more bleeding as a price for obtaining a larger specimen.

We found that bleeding is more likely to occur in patients with definite histologic liver disease. This complements the findings of Perrault who noted that the overall complication rate for liver biopsy was higher in patients with cirrhosis or hepatitis than in those with other disorders.[12] Although our findings might suggest that bleeding is more common because there is a severe structural abnormality of the liver, we think it far more likely that the liver disease causes clotting and other abnormalities which in turn predispose the patient to bleeding.

This study has shown convincingly that relative contraindications to liver biopsy are present more frequently in patients who bleed than in those who do not. This is not to say that all patients with these contraindications will bleed following liver biopsy. To estimate the actual risk of these abnormalities would require liver biopsy in large numbers of patients with one or more contraindications to biopsy. As one small measure of the risk, liver biopsies were done at Stanford (during a six-year period) in 49 patients with a prothrombin time less that 50 percent or a thromboplastin time greater than 10 seconds over control. Three of these 49 patients bled (an incidence of 6.1 percent, a rate which is sixfold higher than the 0.9 percent rate in the remaining 633 patients). Whatever the true risk with these relative contraindications to biopsy, we believe that their presence in any given patient should give pause to those considering this procedure. In that light, it is difficult to see why the clinical diagnosis of alcoholic liver disease or acute viral hepatitis required a liver biopsy in three patients with a documented contraindication. If a liver biopsy is deemed absolutely necessary, it would be wise to correct any clotting abnormalities completely. This was not always done in our patients. We cannot guarantee that doing so would have prevented the bleeding episodes. However, liver biopsies have been carried out safely in patients with hemophilia when their factor deficiencies were fully corrected.[15]

We believe that some of the bleeding episodes in our patients could have been prevented with more careful attention to the indications and contraindications to biopsy, and more vigorous correction of recognized clotting abnormalities.

REFERENCES

1. Edmondson HA, Schiff L: Needle biopsy of the liver, chap 9, *In* Edmondson HA, Schiff L (Eds): Diseases of the Liver, 4th Ed. Philadelphia, JB Lippincott Company, 1975, pp 247-271

2. Terry R: Risks of the needle biopsy of the liver. Br Med J 1:1102-1105, May 1952

3. McCloskey RV, Gold M, Weser E: Bacteremia after liver biopsy. Arch Intern Med 132:213-215, Aug 1973

4. Raines DR, VanHeertum RL, Lawrence FJ: Intrahepatic hematoma: A complication of percutaneous liver biopsy. Gastroenterology 67:284-289, Aug 1974

5. Zamcheck N, Klausenstock O: Liver biopsy (concluded)—II. The risk of needle biopsy. N Engl J Med 249:1062-1069, Dec 1953

6. Linder H: Grenzen und gefahren der Perkutanen Leberbiopsie mit der Menghini-Nadel: Erfahrungen bei 80,000 Leberbiopsien. Deutsch Med Wschr 92:1751-1757, Sep 1967

7. Thaler H: Uber Vorteil und Risiko der Leberbiopsiemethode nach Menghini. Wien Klin Wschr 76:533-538, Jul 1964

8. Menghini G: One second biopsy of the Liver—Problems of its clinical application. N Engl J Med 283:582-585, Sep 1970

9. Brown WB Jr, Hollander M: Statistics, A Biomedical Introduction. New York, John Wiley & Sons, 1977

10. Ovlisen B, Baden H: Liver biopsy by the method of Menghini. Nord Med 83:297-299, Mar 1970

11. Parets A: Detection of intrahepatic metastases by blind needle liver biopsy. Am J Med Sci 237:335-340, Mar 1959

12. Perrault J, McGill DB, Ott BJ, et al: Liver biopsy: Complications in 1000 inpatients and outpatients. Gastroenterology 74: 103-106, Jan 1978

13. Krarup NR: Aspiration biopsy of the liver, with special reference to method of Iversen-Roholm: Survey. Acta Med Scand [Suppl]234:199-209, Nov 1949

14. Lundquist A: Fine-needle aspiration biopsy of the liver: Applications in clinical diagnosis and investigation. Acta Med Scand [Suppl]520:5-28, Jan 1971

15. Spero JA, Lewis JH, VanThiel DH, et al: Asymptomatic structural liver disease in hemophilia. N Engl J Med 298:1373-1378, Jun 1978

Refer to: Knochel JP: Hypophosphatemia (Nutrition in Medicine). West J Med 134:15-26, Jan 1981

Hypophosphatemia

JAMES P. KNOCHEL, MD, *Dallas*

Hypophosphatemia is a common laboratory abnormality that occurs in a wide variety of disorders. When severe and prolonged, it may be associated with rhabdomyolysis, brain dysfunction, myocardial failure and certain defects of erythrocyte function and structure. Other disorders ascribed to hypophosphatemia, including platelet dysfunction and thrombocytopenia, liver dysfunction, renal tubular defects, peripheral neuropathy, metabolic acidosis and leukocyte dysfunction are less well documented. In quantitative terms, the most severe phosphate deficiency is seen in patients who consume a phosphate-deficient diet in conjunction with large amounts of phosphate-binding antacids, in persons with severe, chronic alcoholism and in patients with wasting illnesses who are refed with substances containing an inadequate amount of phosphate. When severe hypophosphatemia occurs in such a setting, the clinical effects appear to be much more pronounced. While there have been some advances in our understanding of the pathophysiology of phosphate depletion and hypophosphatemia, much remains to be learned. Treatment of hypophosphatemia is controversial; however, there is little question that it is indicated in alcoholic patients and those with severe phosphate deficiency.

MODERATE HYPOPHOSPHATEMIA, arbitrarily defined as a serum phosphorus level ranging between 1.0 and 2.5 mg per dl, occurs under numerous circumstances (Table 1). Being a highly reactive ion involved in many chemical reactions, phosphate is readily taken up from extracellular fluid into cells and incorporated into several organic compounds. Persistent moderate hypophosphatemia is an important finding because it may reflect such disorders as vitamin D deficiency, hyperparathyroidism or a reabsorptive defect of the renal tubule. In most instances, hypophosphatemia of itself is no more than an interesting evanescent biochemical bystander. Little difficulty appears to result from moderate hypophosphatemia per se. When concentrations fall below 1.0 mg per dl and remain at that level for two or more days, however, serious consequences may occur.

Dr. Knochel is Chief, Medical Service, Veterans Administration Medical Center, Dallas, and Professor and Vice-Chairman, Department of Internal Medicine, University of Texas Southwestern Medical School, Dallas.

Reprint requests to: James P. Knochel, MD, Chief, Medical Service (111), Veterans Administration Medical Center, Dallas, TX 75216.

Causes of Severe Hypophosphatemia

The conditions associated with severe hypophosphatemia, herein defined as a serum phosphorus level of less than 1 mg per dl, are shown in Table 2. The most common cause of this condition is chronic alcoholism and alcohol withdrawal. Hypophosphatemia is especially common in alcoholic patients in hospital.[1-3] In such patients, serum phosphorus levels may be normal initially but decline to extremely low values after

ABBREVIATIONS USED IN TEXT

ADP = adenosine diphosphate
AMP = adenosine monophosphate
ATP = adenosine triphosphate
CNS = central nervous system
2,3-DPG = 2,3-diphosphoglycerate
LD_{50} = lethal dose, median
P_{50} = partial pressure of oxygen at which hemoglobin is 50 percent saturated

one to three days. With the onset of hypophosphatemia, phosphate in the urine virtually disappears. This presumably indicates cellular uptake of inorganic phosphate as administered nutrients are metabolized. Such severe hypophosphatemia could also be the result of acute respiratory alkalosis. In nearly all cases of severe alcoholism, respiratory alkalosis occurs during withdrawal.[3,4]

Measurement of skeletal muscle composition in patients with severe alcoholism shows that phosphate deficiency almost always exists.[4] The cause of phosphate deficiency in these patients is not completely understood. While one could certainly implicate deficient intake, malnutrition cannot always be shown. Studies in our laboratory on dogs given intoxicating doses of alcohol twice a day for only four weeks showed a substantial reduction of total muscle phosphate despite a nutritious diet and an abundant intake of this mineral.[5]

Ingestion of phosphate-binding antacids such as aluminum hydroxide or aluminum carbonate may cause phosphate depletion and hypophosphatemia. In human volunteers fed a low phosphate diet and large quantities of phosphate-binding antacids, severe hypophosphatemia and phosphate deficiency developed.[6] In most clinical circumstances, ingestion of antacids does not cause phosphate deficiency unless dietary intake of the mineral is severely restricted.

Severe hypophosphatemia has been noted in patients suffering widespread, severe thermal injury. It usually appears during the first few days after the burn.[7] In such patients, phosphate excretion is substantially depressed and respiratory alkalosis is the rule. Some evidence exists suggesting that the incidence of burn wound sepsis may be increased as a result of hypophosphatemia.

Uncontrolled diabetes mellitus with heavy glycosuria is a well-established cause of phosphate depletion. Phosphate is excreted excessively into the urine as a result of osmotic diuresis. In addition, metabolic acidosis depresses phosphorylation, tends to elevate serum phosphorus concentration and thereby intensifies phosphaturia. Thus, severe phosphate deficiency may occur in diabetic ketoacidosis.[1] Administration of insulin and fluids results in a rapid decline of serum phosphorus levels and disappearance of phosphate from the urine. Severe hypophosphatemia is common during recovery from diabetic ketoacidosis.

Administration of calories and other nutrients in excess of requirements to patients who have lost weight may result in severe hypophosphatemia. Their shrunken cells must be capable of an anabolic response. Hypophosphatemia occurs as a result of synthesizing protoplasm with inadequate quantities of phosphate.

The nutritional recovery syndrome represents a constellation of findings observed during the refeeding of patients with severe protein-calorie malnutrition or starvation. In contrast to hyperalimentation, hypophosphatemia may occur during administration of calories *in normally required quantities*. Most observations of this syndrome were made while treating prisoners of war at the end of World War II. Refeeding, especially when simple carbohydrates were given overzealously, was sometimes followed by peripheral edema, ascites and hydrothorax. Sudden death was common. Administration of brewer's yeast did not consistently prevent these complications.[8] However, refeeding with skim milk was apparently

TABLE 1.—*Causes of Moderate Hypophosphatemia*

Hemodialysis	Volume expansion
Hyperparathyroidism	—Aldosteronism (licorice)
Starvation	—Saline infusion
Glucose administration	—Hypokalemia
Fructose administration	Hypomagnesemia
Glycerol administration	Gram-negative bacteremia
Lactate administration	Insulin administration
Sodium bicarbonate infusion	Gastrin administration
Osteomalacia	Glucagon administration
Renal tubular defects	Epinephrine administration
Pregnancy	Corticosteroid administration
Malabsorption	Diuretic therapy
Vitamin D deficiency	Androgen therapy
Acute gout	Recovery from hypothermia
Salicylate poisoning	

TABLE 2.—*Causes of Severe Hypophosphatemia*

Chronic alcoholism and alcoholic withdrawal
Pharmacologic phosphate binding
Severe thermal burns
Recovery from diabetic ketoacidosis
Hyperalimentation
Nutritional recovery syndrome
Respiratory alkalosis
Postrenal transplantation

associated with less morbidity. Unfortunately, obtaining measurements of chemical composition of the blood or urine from those patients was not possible. This syndrome can be reproduced in experimental animals and is commonly seen during overzealous feeding of patients who have lost large quantities of weight as result of food faddism or anorexia nervosa. Based on clinical descriptions, such patients closely resemble the prisoners after World War II. In addition to hypophosphatemia provoked by nutrients, most of these patients show other serious disturbances such as hypokalemia, hypomagnesemia and severe glucose intolerance. The observation that feeding with small quantities of skim milk rather than pure carbohydrates caused less morbidity may very likely be ascribed to the phosphate and potassium content of skim milk.

Severe respiratory alkalosis can cause severe hypophosphatemia. Studies of normal subjects have shown that serum phosphorus concentrations may fall below 0.5 mg per dl after voluntary hyperventilation.[9,10] Respiratory alkalosis is probably one of the most common causes of severe hypophosphatemia in patients in hospital. Hyperventilation may apparently accompany metabolic encephalopathy resulting from alcoholic withdrawal, or simply may be the result of fear and pain. Respiratory alkalosis can be especially prominent in patients with sepsis and bacteremia. The mechanism of hypophosphatemia under such conditions is clear. Reduction of carbon dioxide in the blood is associated with an equally rapid reduction of carbon dioxide in the cells. The associated elevation of intracellular pH activates phosphofructokinase which in turn accelerates phosphorylation of glucose[11]; phosphate ions are rapidly taken up from serum and hypophosphatemia results. Simultaneously, phosphate virtually disappears from the urine. On the other hand, if an equal degree of alkalosis is induced by infusing sodium bicarbonate, serum phosphorus concentration falls only slightly and excretion of phosphate in the urine *increases*.[10] The increase of phosphate excretion occurs by two mechanisms. First, a slight expansion of extracellular fluid volume occurs as a result of bicarbonate infusion and this reduces reabsorption of phosphate in the proximal tubule. Second, because of plasma volume expansion and a slight reduction of serum calcium concentration, parathyroid hormone levels increase during bicarbonate infusion and serve to decrease tubular reabsorption of phosphate.

TABLE 3.—*Consequences of Severe Hypophosphatemia*

Rhabdomyolysis
Erythrocyte dysfunction and hemolysis
Myocardial dysfunction
Leukocyte dysfunction
Platelet dysfunction
Central nervous system dysfunction
Metabolic acidosis
Osteomalacia

Severe hypophosphatemia has also been noted in some patients who have had renal transplants. Such patients apparently have a renal tubular reabsorptive defect that permits excessive loss of phosphate into the urine. This has often occurred during corticosteroid therapy and administration of phosphate-binding antacids, both of which could conceivably favor development of hypophosphatemia.

Consequences of Acute Hypophosphatemia

Current evidence suggests that there are at least eight definite harmful consequences of severe hypophosphatemia. These are illustrated in Table 3. That other tissues, organs or physiological functions are affected appears likely.

Rhabdomyolysis

Rhabdomyolysis, or acute necrosis of skeletal muscle, is one of the most common and reproducible consequences of phosphate deficiency and severe hypophosphatemia. In most cases it is recognized by the appearance of abnormal elevations of muscle enzymes in serum, such as creatine phosphokinase or aldolase. When severe, it may be associated with overt physical findings of muscle necrosis, including profound weakness, pain, stiffness, tenderness and edema of involved muscles and, sometimes, the appearance of myoglobin in the urine. In most cases of hypophosphatemia, rhabdomyolysis is clinically mild or asymptomatic and reflected only by elevated levels of muscle enzymes. This occurs most commonly in persons with chronic alcoholism; however, it has also been seen in patients who become hypophosphatemic as a result of hyperalimentation for weight loss. It is rarely observed during recovery from diabetic ketoacidosis. Measurement of muscle composition in such patients has invariably shown severe deficiency of phosphate. At least in patients with chronic alcoholism, phosphate deficiency occurs in association with other disturbances, including mag-

nesium deficiency and, in some but certainly not all cases, a moderately low content of potassium. Tissue content of sodium, chloride, water and calcium is nearly always substantially elevated in such patients.[1] To my knowledge, there have been no reports of rhabdomyolysis with severe hypophosphatemia as a result of respiratory alkalosis if body stores of phosphate are normal. Experimental studies on dogs support this observation. On the other hand, a reversible electrochemical defect of skeletal muscle cells appears after feeding a diet containing all essential nutrients except phosphate. This defect is reversible on repletion with phosphate. However, if an animal with preexisting phosphate deficiency is subjected to hyperalimentation without phosphate, hypophosphatemia is promptly induced, and severe rhabdomyolysis supervenes.[12,13] Dogs fed intoxicating doses of ethanol each day will eventually show depletion of skeletal muscle phosphate despite an adequate phosphate intake.[14]

Erythrocytes in Hypophosphatemia

The most important biochemical abnormalities of erythrocytes associated with phosphate deficiency and severe hypophosphatemia include a decline of 2,3-diphosphoglycerate (2,3-DPG) and a decline of adenosine triphosphate (ATP).[15] Inorganic phosphate in erythrocytes is in diffusion equilibrium with plasma phosphate. Consequently, both 2,3-DPG and ATP may become reduced in the presence of severe hypophosphatemia.

An important interaction occurs between hemoglobin and 2,3-DPG that promotes release of oxygen.[16] This has been quantitated by means of the index, P_{50}, which is a value for oxygen tension of mixed venous blood at 37°C, pH 7.4, at which hemoglobin is 50 percent saturated. Low levels of 2,3-DPG may depress P_{50} values or shift the oxyhemoglobin saturation curve to the left so that release of oxygen to peripheral tissues is diminished. Thus, acute hypophosphatemia, when associated with a serious decline of 2,3-DPG may limit release of oxygen at the cellular level and thereby create anoxia. The interaction of hemoglobin with 2,3-DPG occurs at the same molecular site of hemoglobin glycosylation in patients with persistent hyperglycemia. It is possible, therefore, that a potentiation of impaired oxygen delivery could occur in phosphate deficient, hypophosphatemic and persistently hyperglycemic patients with diabetes mellitus. An additional potentiating factor in patients with diabetes could be the presence of metabolic acidosis. This would favor decomposition of 2,3-DPG, independent of hyperglycemia or phosphate deficiency.

Structural defects of erythrocytes in phosphate deficiency and hypophosphatemia include increased rigidity and in rare instances hemolytic anemia.[17,18] Hemolysis has also been described in patients with chronic uremic acidosis in whom serum phosphorus has been profoundly depressed by excessive ingestion of phosphate-binding antacids.[15,18,19] Hemolysis is actually a rare complication of severe hypophosphatemia. When it has occurred, ATP content has invariably been less than 15 percent of normal. Hemolysis is usually provoked by an unusual stress on the metabolic requirements of erythrocytes such as severe metabolic acidosis.

Myocardial Dysfunction

If phosphate deficiency and hypophosphatemia were sufficiently severe to reduce the content of 2,3-DPG in erythrocytes, one might predict that release of oxygen to tissues would diminish as a result of shifting the oxyhemoglobin dissociation curve to the left and, in response, the resting cardiac output would necessarily rise. One might further speculate that if a high resting cardiac output occurred by this means, such a condition, especially in a case of severe alcoholism, might lead one to suspect underlying vitamin deficiency and beriberi heart disease. However, data are not available to verify such speculations.

Fuller has examined the effects of pure phosphate deficiency on myocardial performance in dogs.[12,20] These animals were gavage-fed a diet that was normal in all respects except that it contained only trace quantities of phosphate. Transducers were implanted surgically for measurement of ascending aortic root blood velocity and left ventricular pressure. The dogs were studied while awake. Their serum phosphorus values had fallen from 5.1 to 0.9 mg per dl and muscle phosphate concentration had fallen from 28 to 22.6 mmoles per 100 grams fat free dry weight. When phosphate deficiency existed, stroke volume, peak blood flow velocity, maximum ascending aortic blood flow acceleration and maximum left ventricular rate of change of pressure (dp/dt) had decreased significantly. Restoration of phosphate to the diet corrected all of these abnormalities. Although the relationship between 2,3-DPG in

erythrocytes and oxyhemoglobin dissociation may not be the same in dogs as in humans, it was clear that experimental phosphate deficiency and hypophosphatemia resulted in a hypodynamic effect on the heart rather than the speculated high-output state.

Somewhat similar observations have been made by O'Connor and his co-workers[21] regarding critically ill patients whose average serum phosphorus concentration was 0.97 mg per dl (range 0.7 to 1.4 mg per dl). After infusing 1,000 mg of phosphorus (as phosphate) in 60 ml of fluid volume, cardiac output did not change significantly but calculated stroke work rose. The latter occurred independently of Starling effects and probably represented an improvement in myocardial contractility.

Perhaps the most important clinical observations to date on hypophosphatemic cardiomyopathy were made by Darsee and Nutter.[22] They studied the cases of three patients with severe congestive cardiomyopathy and florid heart failure. In the first patient, who was alcoholic, the serum phosphorus level was 0.4 mg per dl. In the second, a 42-year-old man who had ingested large quantities of aluminum hydroxide gel for several months, the serum phosphorus level was 0.6 mg per dl. In the third patient the serum phosphorus level was 0.3 mg per dl, and aluminum hydroxide gel also had been consumed. All three patients recovered completely from their congestive cardiomyopathy following restoration of serum phosphorus levels to normal. Of importance, only the first patient received digitalis and diuretics, the second and third patients did not. These observations suggest that correction of hypophosphatemia itself reversed cardiomyopathy.

Although severe hypophosphatemia occurs commonly in a wide variety of circumstances, recognition of congestive cardiomyopathy or overtly impaired ventricular function in hypophosphatemia is highly unusual. The reason for this may be explained by preliminary experimental studies from two different laboratories. In our laboratory we have examined the effects of hyperalimentation-induced hyposphatemia on dogs whose weight had been reduced by caloric restriction. Despite an appreciable fall of skeletal muscle phosphate content during hyperalimentation, myocardial content of inorganic phosphate, ATP, adenosine diphosphate (ADP) and total phosphorus remained within normal limits. These findings existed in the face of serum phosphorus concentrations of less than 1 mg per dl. These findings suggest that the heart, being vital to life, has protective mechanisms that maintain vital energy substrates at the expense of skeletal muscle.

Darsee has also examined this problem in rats maintained on a phosphate-free diet and phosphate-binding antacids for seven weeks.[23] Although levels of serum and skeletal muscle phosphorus were depressed significantly, cardiac muscle phosphate levels were normal. Preliminary studies in their laboratories suggested that the clinical appearance of hypophosphatemic cardiomyopathy was usually preceded by an event that caused sudden release of residual myocardial phosphate into the blood stream. In experiments using dogs, they showed that following ten minutes occlusion of the midportion of the left anterior descending coronary artery, myocardial contractility was substantially decreased in phosphate-depleted dogs but not in normal dogs with the same duration of coronary occlusion. Such findings might mean that although total phosphate, inorganic phosphate and perhaps even the adenylic acid pool remain normal in hearts of phosphate-deficient dogs, the metabolic state and potential contractility of the myocardium are extremely tenuous and fail with insults that would not ordinarily affect muscle performance.

Increased attention should be paid to the effects of phosphate deficiency on the heart. Although frank congestive cardiomyopathy under such conditions appears to be rare, it nevertheless appears to be one of the few types of congestive cardiomyopathy that is curable.

Leukocyte Function During Hypophosphatemia

A serious complication of intravenous hyperalimentation therapy is systemic infection by bacterial and fungal organisms. Hypophosphatemic dogs show severe depression of chemotactic, phagocytic and bactericidal activity of granulocytes. These abnormalities are reversed on correction of hypophosphatemia.[24] Similar observations have been made on a patient who became hypophosphatemic during hyperalimentation.[18]

Respiratory alkalosis and hypophosphatemia may occur in association with Gram-negative bacteremia.[25] Guinea pigs infected with *Salmonella* organisms became hypophosphatemic before death. When given phosphate, however, mortality was substantially reduced and fewer organisms were found in their tissues.[26]

Apparently, hypophosphatemia impairs granu-

locyltic function by disrupting ATP synthesis. ATP provides energy for contractions of microfilaments, which in turn regulate the mechanical properties of leukocytes—namely, pseudopod and vacuole formation.[27]

Platelet Function During Hypophosphatemia

Seven abnormalities of platelet function and structure have been observed in hypophosphatemic dogs: (1) thrombocytopenia, (2) increased platelet diameter suggesting shortened platelet survival, (3) megakaryocytosis of the marrow, (4) a fivefold to tenfold acceleration in rate of disappearance of labeled platelets from blood, (5) impairment of clot retraction, (6) a 44 percent reduction in platelet ATP content and (7) hemorrhaging into the gut and skin. These abnormalities can be circumvented if phosphate supplements are provided.[28] Similar changes have not been observed in humans.

Effects of Hypophosphatemia on the Central Nervous System

Some patients with severe hypophosphatemia have symptoms compatible with a metabolic encephalopathy.[18,29] In sequence, irritability, apprehension, weakness, numbness, paresthesias, dysarthria, confusion, obtundation, convulsive seizures and coma occur. This clinical syndrome has been observed in patients without other apparent causes for encephalopathy who have received intravenous hyperalimentation therapy as well as in patients during withdrawal from chronic alcoholism. In contrast to delirium tremens, hallucinations have not been observed. Obviously, both conditions may coexist.

The relationship between hypophosphatemia and the decline of erythrocyte 2,3-DPG becomes especially important in tissues where oxygen is necessary for energy production. This could have an important role in the brain where oxidation of glucose through the Krebs cycle is necessary for synthesis of ATP.

In one report,[18] it was found that in three of the eight patients who became hypophosphatemic during hyperalimentation, paresthesias, mental obtundation and hyperventilation developed. In those whose P_{50} values were abnormally low there was diffuse slowing in the frequency of electrical impulses on their electroencephalograms. These changes disappeared when hypophosphatemia was corrected. Perhaps the best evidence that hypophosphatemia plays a role in this encephalopathy has been the observation that it does not occur in patients receiving hyperalimentation with adequate phosphate.

Metabolic Acidosis

Substantial clinical and experimental evidence is now available indicating that severe metabolic acidosis may occur in the presence of phosphate deficiency and severe hypophosphatemia. When phosphate is removed from the diet or its absorption is prevented by binding with antacids, bone minerals are promptly mobilized. This apparently occurs even before the advent of hypophosphatemia and suggests operation of an unidentified hormone. Phosphate deficiency in a child, or in an adult who has a disease process causing rapid turnover of bone, may cause hypercalcemia. Independently of hypercalcemia, phosphate deficiency nearly always causes hypercalciuria. Phosphate deficiency thus induced is seldom associated with metabolic acidosis. However, as hypophosphatemia becomes more severe, phosphate ions virtually disappear from the urine thereby eliminating the capacity to excrete metabolic hydrogen as titratable acid. The bulk of metabolic acid is excreted by exchange of hydrogen ions ($H+$) from the cell with sodium ions ($Na+$) from the renal tubular lumen. In this process, Na_2HPO_4 is converted to NaH_2PO_4 and the hydrogen ions are measurable as titratable acid. If phosphate is absent from the urine, metabolic acid can be excreted by the reaction $NH_3 + H^+ \rightleftharpoons NH_4^+$. Ordinarily, a decline of intracellular pH would augment production of ammonia (NH_3). However, in phosphate deficiency, it has been proposed that intracellular pH rises, thereby decreasing NH_3 production. A rise of intracellular pH in phosphate deficiency has been shown to occur in liver and muscle.[30] Whether similar changes occur in the kidney cell has not been determined. Nevertheless, abundant evidence shows that phosphate deficiency reduces ammonia excretion and thus supports the theory that the intracellular pH of renal cells rises. Thus, the decrease in ammonia production and unavailability of buffer phosphate in the urine essentially prevent excretion of metabolic acids.

The question arises as to why profound metabolic acidosis does not regularly develop in persons who cannot excrete titratable acid or form ammonium. The explanation lies in the fact that during mobilization of bone mineral, there also occurs mobilization of carbonate, which is an im-

portant component of bone apatite (Figure 1). Sufficient carbonate is mobilized from bone to titrate metabolic acid. In fact, in studies using animals it has been found that carbonate mobilization may overshoot and result in slight metabolic alkalosis. However, should some event occur that prevents mobilization of bone mineral, metabolic acidosis of severe proportion can occur. This has been described in children with severe lactase deficiency and protein-calorie malnutrition during refeeding without adequate phosphate. Addition of phosphate to their dietary mixture resulted in pronounced increments of acid excretion into the urine and correction of metabolic acidosis. Experimentally, bone mobilization resulting from phosphate deficiency also prevents metabolic acidosis. However, metabolic acidosis rapidly supervenes if agents are administered that interrupt mobilization of bone mineral such as diphosphonate or colchicine.[31] Although it might be possible that the mild state of hyperchloremic metabolic acidosis that regularly occurs during recovery from diabetic ketoacidosis is a result of phosphate deficiency and hypophosphatemia, there is no evidence to support this notion.[32]

Besides the metabolic interplay of bone mineral mobilization and altered excretion of acid by the kidney, there also may occur a depression of bicarbonate reabsorption in the proximal tubule.[30,33] However, Schmidt[34] was unable to reproduce these findings. The potential clinical importance of proximal tubular bicarbonate wasting in phosphate depletion has not been established.

Osteomalacia

Mobilization of bone mineral during phosphate deficiency and hypophosphatemia, when present for a sufficiently long time, may result in clinically evident osteomalacia. Such a condition has been described by Cooke and her associates.[35] Their patient had ingested a diet deficient in phosphate and had consumed large quantities of phosphate-binding antacids for a prolonged time. In the classic studies conducted by Lotz and Barrter,[6] dietary deprivation of phosphate and ingestion of phosphate-binding antacids was associated with hypercalciuria. When serum phosphorus levels approached 1 mg per dl or less, the patients complained of weakness and bone pain and were thought to have all of the clinical features of osteomalacia. However, their symptoms were relieved promptly on restoration of phosphate to their diets and elimination of phosphate-binding

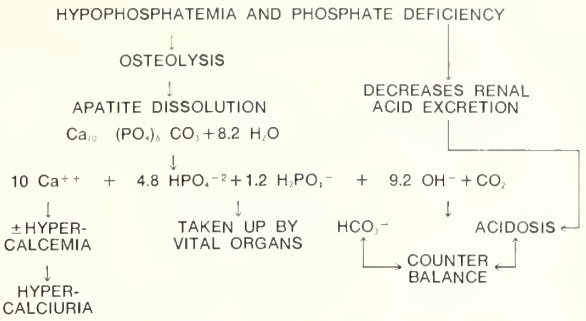


Figure 1.—Deprivation of phosphate stimulates dissolution of the skeleton in an apparent attempt to maintain a normal serum phosphorus concentration. Apatite breaks down to calcium, phosphate, carbonate and water. Hypercalcemia occurs in children or in any person if increased bone turnover prevails. Hypercalciuria is a regular feature. Although urine phosphate is sufficiently depressed to prevent acid excretion as titratable acidity, carbonate ions mobilized from apatite titrate the retained metabolic acids sufficiently to prevent metabolic acidosis. If this process is long-standing, classic osteomalacia may result.

antacids. Hypercalciuria appears to be an aspect of phosphate deficiency found more often in women than in men.[36]

Unproved Consequences of Hypophosphatemia

Because adequate supplies of inorganic phosphate are critical for repletion of ATP stores in every cell, it seems conceivable that any tissue or organ may become damaged in the presence of severe hypophosphatemia. Descriptions of muscular paralysis independent of rhabdomyolysis have appeared.[37,38] Unfortunately, the patients in one report[38] were also acutely hypokalemic. Thus, the role of hypophosphatemia was unclear. That hepatocellular dysfunction might occur in severe hypophosphatemia was first suggested by Frank and Kern in 1962.[39] They described a 51-year-old woman with alcoholic cirrhosis whose serum phosphorus level had fallen to 0.5 mg per dl in the wake of respiratory alkalosis. Her bilirubin level rose appreciably and she became comatose. During the following few days her serum phosphorus levels returned to normal and abnormal neurological findings cleared. We have also observed this sequence of events in alcoholic patients in hospital and, therefore, question the possibility that spontaneous correction of hypophosphatemia by release of phosphate from injured skeletal muscle may be inadvertently life-saving in such patients.

Severe hypophosphatemia may alter the redox (reduction-oxidation) state of cytosol and con-

ceivably be responsible for lactic acidosis or β-hydroxybutyric ketoacidosis.[40] Unfortunately, studies have not been conducted to determine if pancreatitis or even intestinal function could be impaired by hypophosphatemia.

Mechanism of Cellular Injury in Hypophosphatemia

In hypophosphatemia and phosphate deficiency, critical determinants of cellular injury appear to be the prevailing concentration of inorganic phosphate and adenine nucleotides in the cytosol. In particular, if the concentration of cytosolic ATP falls to a critically low level, cellular dysfunction or disintegration may follow. The supply of inorganic phosphate in the cytosol is critical for resynthesis of ATP from ADP.[41]

Unquestionably, combined phosphate deficiency and severe hypophosphatemia can result in widespread cellular damage. On the other hand, whether hypophosphatemia independent of phosphate deficiency can induce cellular damage or dysfunction is unclear. One study, published in abstract form only, showed that experimental animals given *Salmonella* organisms intravenously became hypophosphatemic as the result of respiratory alkalosis.[26] When sufficient phosphate to prevent hypophosphatemia was given along with the same dose of bacteria, the LD_{50} (lethal dose, median) was significantly increased. Similarly, prevention of severe hypophosphatemia may reduce the incidence and morbidity from burn wound sepsis and bacteremia in patients with severe thermal burns (D. Haburchak, US Army, Institute for Surgical Research, Fort Sam Houston, TX, oral communication, June 1978).

Energy requirements to maintain cellular function and integrity may undergo rapid fluctuation, and these variable demands must be integrated and transmitted to mitochondria where energy is produced. At any given instant, the mitochondrial respiratory rate must respond to these minute-to-minute changes in cellular demands. This cellular energy state is reflected by several substrate concentration ratios.[42] For example, the lactate to pyruvate ratio indicates the cytosolic redox state, while that of mitochondria is reflected by the ratio of β-hydroxybutyrate to acetoacetate. However, the overall energy state of the cell is perhaps best represented by the phosphorylation potential.[43] This is defined as the ratio of cytosolic ATP to the product of cytosolic ADP and inorganic phosphate:

$$\text{Phosphorylation potential} = \frac{[ATP]}{[ADP]\times[P^i]}$$

Any metabolic alteration that increases the value of the phosphorylation potential slows mitochondrial respiration. In contrast, if the phosphorylation potential decreases, mitochondrial respiration accelerates. Thus, a reduction of cytosolic inorganic phosphate increases the potential and slows mitochondrial respiration. By this mechanism, ATP levels fall and reduce the ATP to ADP ratio, thereby normalizing the phosphorylation potential.

Besides affecting the mitochondrial respiratory rate,[44] intracellular inorganic phosphate concentration is also an important regulator of the overall adenine nucleotide pool size. ADP, AMP (adenosine monophosphate) and ATP are in equilibrium through the myokinase reaction:

$$2\ ADP \rightleftharpoons AMP + ATP$$

A major degradation pathway for the adenylate pool is the irreversible deamination of AMP to inosine monophosphate (IMP) catalyzed by the enzyme AMP-deaminase. This reaction is strongly inhibited by a normal concentration of intracellular phosphate. Thus, a pronounced reduction in intracellular phosphate deinhibits AMP-deaminase, resulting in AMP degradation and is in turn reflected throughout the adenylate pool. This phenomenon is exemplified by the response to intravenously given fructose.[45] Fructose is metabolized by three tissues: intestinal mucosa, liver and renal cortex. Its phosphorylation by these tissues is facilitated by fructokinase. Formation of fructose phosphate is unregulated, meaning that increasing concentrations of fructose phosphate in the cytosol do not inhibit further uptake of fructose. Thereby, the cytosolic concentration of inorganic phosphate is sharply lowered, AMP-deaminase is deinhibited and the adenylate pool is reduced. In patients with hereditary fructose intolerance, the product of AMP deamination, inosine, and its product, uric acid, appear in the urine in increased quantities following administration of fructose.[46] This reaction is illustrated as follows:

$$\begin{array}{l} 2\ ADP \rightarrow ATP + AMP \\ \qquad\qquad \downarrow \quad (\text{Low } P^i) \quad \left\{ \begin{array}{l} \text{Fructose} \\ \text{Fructose phosphate} \end{array} \right. \\ \qquad\qquad IMP \\ \qquad\qquad \downarrow \\ \qquad\qquad \text{Urate} \end{array}$$

This sequence of events occurs very rapidly and has been associated with functional and structural disturbances in the liver and kidney.[47] Adminis-

tration of inorganic phosphate provides partial protection against these harmful effects.

A sustained, severe reduction of inorganic phosphate concentration in the cells will reduce the cytosolic concentration of ATP. This can potentially result in a critical deficiency of ATP for energy-requiring reactions. The fall of ATP concentration activates 5′ nucleotidase which has an additional "self-destructive" effect by further reducing the adenylic acid pool.

Although information is not complete, certain tissues appear to be more susceptible to hypophosphatemia than others. For example, intracellular concentration of inorganic phosphate in erythrocytes is dependent on diffusion down a chemical gradient from plasma (in other words, in order for phosphate to enter the erythrocyte, the phosphate concentration in plasma must exceed that in cytoplasm). Thus, hypophosphatemia leads to a reduction of cellular inorganic phosphate, and this in turn reduces the cell's capacity to produce ATP. This process, apparently, would be independent of the reduced 2,3-DPG, which in turn would alter the cell's capacity to release oxygen. If an additional metabolic stress is superimposed, such as severe acidosis, hemolysis may occur.[27] Hemolysis has been observed only when ATP concentrations have fallen to very low values. In contrast to the erythrocytes, other tissues apparently have the capacity to maintain more adequate supplies of intracellular inorganic phosphate despite hypophosphatemia. In our own studies,[48] dogs were fed a calorie-restricted diet containing abundant phosphate. When their baseline body weight had been reduced by a third, hyperalimentation was carried out without adequate phosphate until their serum phosphorus levels fell to 1.0 mg per dl or less. Although total muscle phosphate fell rapidly during hyperalimentation, muscle inorganic phosphate concentration remained normal as also did the concentrations of ATP and ADP. Thus, both the phosphorylation potential and the adenylate pool remained normal. These observations suggest that retention of inorganic phosphate by muscle despite hypophosphatemia represents a fundamental, vital process to maintain cellular integrity.

Another investigator has examined skeletal muscle inorganic phosphate, ATP and ADP concentrations in dogs with chronic phosphate deficiency (T. J. Fuller, MD, University of Florida, Gainesville, unpublished observation, 1979). Each component fell by approximately 50 percent. The phosphorylation potential became twice normal, indicating that the cell's capacity to produce ATP was reduced. Because the content of ATP is low, such a cell is in a state of peril should there appear a demand for energy production. For example, if inorganic phosphate cannot be maintained in the face of acute hypophosphatemia, ATP levels would decrease further and disintegration might follow.[41] Fuller's findings probably explain why superimposition of severe hypophosphatemia on a cell already injured by chronic phosphate deficiency causes florid rhabdomyolysis[13] and perhaps explain why papillary muscles of phosphate-deficient rats fail to recover after an ischemic interval.[23]

It would seem possible that cells injured by a variety of noxious agents or conditions (such as ethanol, malnutrition, acute starvation, uremia, anoxia or a host of metabolic derangements) could be easily destroyed in the event of severe hypophosphatemia. A preceding injury would only need to compromise those mechanisms responsible for maintaining an optimal concentration of inorganic phosphate in the cell. Thereby, both energy production and the adenylate pool would become inadequate to sustain vital cellular functions.

Treatment of Acute Severe Hypophosphatemia

In any discussion of treatment, the issue of efficacy should be given first consideration. Thus, what evidence exists showing that prevention or treatment of hypophosphatemia is beneficial?

Clinical Evidence

Several older as well as more recent studies provide strong support that correction of phosphate deficiency and hypophosphatemia may be important. Many years ago Friedländer studied cases of diabetes mellitus and found that simultaneous administration of phosphate salts with glucose improved glucose utilization.[49] DeFronzo and Lange[5] recently carried out studies in patients with chronic phosphate deficiency and mild hypophosphatemia that resulted from renal tubular disorders or vitamin D resistant rickets. Each of the patients had impaired glucose utilization. Employing the glucose clamp technique, the study showed that glucose intolerance was not the result of impaired insulin secretion but the consequence of impaired tissue sensitivity to insulin. The effect of phosphate repletion was not examined. Franks

and his associates[50] compared two groups of patients with diabetic ketoacidosis. When phosphate salts were administered in association with conventional therapy, recovery was hastened.

The central nervous system complications of acute severe hypophosphatemia observed during hyperalimentation of wasted patients do not occur if adequate phosphate is provided to prevent hypophosphatemia. Brain dysfunction, electroencephalographic abnormalities and decreased erythrocyte 2,3-DPG content revert to normal if hypophosphatemia is corrected.[18]

Patients with hereditary fructose intolerance show sharp increments in the excretion of inosine and uric acid after challenge with fructose.[46] Administration of phosphate supplements with fructose reduces excretion of both inosine and uric acid. These observations suggest that cytosolic depletion of inorganic phosphate and depletion of the adenylic acid pool are both attenuated in these patients by administration of phosphate.

Administration of calories without adequate phosphate during refeeding therapy led to the rapid development of severe metabolic acidosis in children with protein-calorie malnutrition due to lactase deficiency.[51] However, phosphate supplementation resulted in a sharp increase of titratable acid in the urine and rapid correction of metabolic acidosis.

Finally, Darsee and Nutter[22] and O'Connor and his associates[21] have shown, respectively, improvement in congestive cardiomyopathy and calculated ventricular work associated with profound hypophosphatemia following administration of phosphate salts. In Darsee's patients, recovery occurred without simultaneous administration of digitalis or diuretics.

Experimental Evidence

Abundant experimental evidence indicates that prevention or treatment of hypophosphatemia may be advantageous. Morris and his associates[47] studied the effect of fructose-loading in rats. The decline of ATP, ADP and inorganic phosphate in liver and renal cortical tissue was substantially less if fructose was given with phosphate.

In our own studies the acute florid rhabdomyolysis produced by hyperalimentation of partially starved, phosphate-deficient dogs did not occur if large quantities of inorganic phosphate were added to the hyperalimentation mixture to prevent hypophosphatemia.[13] When hyperalimented without phosphate, the same animals displayed pronounced weakness, tremors, fasciculations and, in many instances, convulsions before death. None of these events occurred when adequate phosphate supplementation was provided.

In experiments involving chronic phosphate-deficient dogs, studies of skeletal muscle showed a rise of sodium chloride content and water, and a decrease in the transmembrane-resting electrical potential difference. Restoration of inorganic phosphate to the diet led to correction of these abnormalities.[12] And in another study, impaired contractile force and decreased left ventricular ejection rates in phosphate-deficient dogs were effectively reversed by phosphate repletion.[20]

Finally, guinea pigs administered graded doses of *Salmonella* organisms regularly became hypophosphatemic as a result of hyperventilation and respiratory alkalosis. The LD_{50} was increased by administration of sufficient phosphate to prevent hypophosphatemia.[26]

The foregoing is considered to be persuasive clinical and experimental evidence that treatment of phosphate deficiency and hypophosphatemia is not only important but effective. However, in those situations where tissue destruction has already occurred, benefit would not be expected. A review has been published offering recommendations for management of phosphate deficiency and hypophosphatemia.[52]

General Management

The general principles of management for phosphate deficiency and hypophosphatemia are similar to those for deficiency of many other ions or minerals. First, if a person can tolerate oral administration of the supplement, it should be administered by this route. Milk is an excellent source of phosphate as well as of potassium and calcium. Its phosphate content is approximately 33 mmoles per quart. In some cases, however, patients with severe phosphate deficiency cannot tolerate lactose or fat. Therefore, if milk cannot be used one might attempt administration of buffered sodium phosphate orally. In the presence of phosphate deficiency and otherwise normal intestinal function, the capacity for phosphate absorption may be enhanced so that the usual expectation of diarrhea with administration of sodium phosphate salts does not occur.

In most instances of severe hypophosphatemia it is necessary to administer phosphate salts intravenously. One should select an intravenous preparation, become acquainted with its contents and,

ideally, administer the compound in a quantity that will not produce hyperphosphatemia. Hypocalcemia and metastatic calcification are distinct hazards of intravenous administration of phosphate salts. Two recent publications studied this problem in children undergoing treatment for diabetic ketoacidosis.[53,54] A special problem may also exist in patients who are simultaneously hypophosphatemic, hypokalemic and hypomagnesemic. Infusion of phosphate (PO_4) salts will lower ionized calcium if the product of calcium and phosphorus exceeds 2.4 to 2.5×10^{-6} moles per liter (58 mg per dl). Herbert and his associates[55] examined the effect of infusing 1.8 mmoles of PO_4 per kg of body weight into normal subjects and observed a fall of serum calcium that averaged 0.18 mmole per liter (-0.7 mg per dl). In one patient with hypoparathyroidism, 1.3 mmoles of PO_4 per kg of body weight reduced serum calcium from 2.1 to 1.8 mmoles per liter (-1.2 mg per dl). If serum calcium is low before administration of PO_4 salts, an appreciable fall of serum calcium would not be anticipated if the solubility product were not exceeded. In healthy subjects, a fall of calcium produced by PO_4 infusion would be in part corrected by release of parathyroid hormone. However, if a patient also has hypomagnesemia, release of parathyroid hormone would be suppressed[56] and, in turn, hypocalcemia could conceivably become more severe and prolonged. Alkalosis could potentiate the tendency for formation of calcium phosphate and thereby enhance hypocalcemia.

Patients being treated for diabetic ketoacidosis, alcoholic patients in withdrawal and patients with steatorrhea often have hypophosphatemia, hypomagnesemia, hypocalcemia and hypokalemia. In such patients, electrolyte replacement solutions should include phosphate, magnesium and potassium. However, lest the conclusion be made that it might be best to avoid phosphate altogether, the natural course of diabetic ketoacidosis should be considered.

Without phosphate treatment, Martin and his co-workers[57] found that 73 percent of adults treated for diabetic ketoacidosis became hypocalcemic and 55 percent became hypomagnesemic. In Zipf's study,[53] nine children with diabetic ketoacidosis were given phosphate salts, and five became hypocalcemic. In the latter study, hypomagnesemia was present in each patient, but fell below 1 mEq per liter in only one. The dosage of phosphate in the children who had the most severe hypocalcemia was greater than 11 mmoles per kg of body weight per 24 hours. Serum phosphorus was also high. Winter and his co-workers[54] described a 9-year-old child with diabetic ketoacidosis in whom hypocalcemia and hypomagnesemia developed after administration of more than 5 mmoles of phosphate per kg of body weight in 29 hours. Based upon such data, hypocalcemia occurs in most patients during treatment of diabetic ketoacidosis whether or not phosphate is given. In addition, if large doses of phosphate are given, hypocalcemia can be seriously aggravated.

In treating adult patients with hypophosphatemia, a rule of thumb that continues to be successful in our patients is administration of approximately 20 mmoles of sodium phosphate intravenously each eight hours. Using this formula, the total daily dose is less than 1 mmole per kg of body weight. This amount has generally been adequate to maintain serum phosphorus levels of at least 1.5 mg per dl. This concentration appears to prevent most of the severe consequences of hypophosphatemia and at the same time should be sufficiently low to prevent hyperphosphatemia and precipitation of calcium phosphate in tissues.

If confronted with the complex electrolyte derangements as described in cases of alcoholic withdrawal, it is practical to administer phosphate, magnesium and potassium in the same solution. For example, we have used solutions composed of 1 liter of 5 percent glucose in 0.45 percent saline, to which have been added 20 mmoles of potassium phosphate, 20 mEq of potassium chloride and 20 ml of 50 percent magnesium sulfate (16 mEq of magnesium). This quantity is infused over eight hours. We have infused this mixture three times a day for several days in many patients with successful results. The three electrolytes are compatible in solution. Used in such quantities, we have not encountered severe hypocalcemia. Obviously, intravenously given phosphate should not be administered in the presence hyperphosphatemia.

REFERENCES

1. Knochel JP: The pathophysiology and clinical characteristics of severe hypophosphatemia. Arch Int Med 137:203-220, 1977

2. Ryback RS, Eckardt MJ, Pautler CP: Clinical relationships between serum phosphorus and other blood chemistry values in alcoholics. Arch Int Med 140:673-677, 1980

3. Knochel JP: Hypophosphatemia in the alcoholic: Arch Intern Med 140:613-615, 1980

4. Anderson R, Knochel JP: J Min Elect Metab (In Press)

5. DeFronzo R, Lange R: Hypophosphatemia and glucose intolerance: Primacy of insulin resistance. Clinical Res 28(2):258A, 1980

6. Lotz M, Zisman E, Bartter FC: Osteomalacia and debility resulting from phosphorus depletion. Trans Assoc Am Physicians 77:281-295, 1964

7. Aubert P, Saizy R, Milhaud G, et al: PTH determinations in hypophosphatemia of sevcrely burned patients, *In* Massry SG, Ritz E, Jahn H (Eds): Phosphate and Minerals in Health and Disease. New York, Plenum Press, 1980

8. Schnitker MA, Mattman PE, Bliss TL: A clinical study of malnutrition in Japanese prisoners of war. Ann Intern Med 35: 69-96, 1951

9. Okel BB, Hurst JW: Prolonged hyperventilation in man: Associated electrolyte changes and subjective symptoms. Arch Intern Med 108:757-762, 1961

10. Mostellar ME, Tuttle EP Jr: The effects of alkalosis on plasma concentration and urinary excretion of inorganic phosphate in man. J Clin Invest 43:138-149, 1964

11. Uyeda K, Racker E: Regulatory mechanisms in carbohydrate metabolism—VII. Hexokinase and phosphofructokinase. J Biol Chem 240:4682-4688, 1965

12. Fuller TJ, Carter NW, Barcenas C, et al: Reversible changes of the muscle cell in experimental phosphorus deficiency. J Clin Invest 57:1019-1024, 1976

13. Knochel JP, Barcenas C, Cotton JR, et al: Hypophosphatemia and rhabdomyolysis. J Clin Invest 62:1240-1246, 1978

14. Blachley J, Ferguson E, Carter N, et al: Chronic alcohol ingestion induces phosphorus deficiency and myopathy in the dog. Trans Assoc Am Physicians, 1980 (In Press)

15. Lichtman MA, Miller DR, Freeman RB: Erythrocyte adenosine triphosphate depletion during hypophosphatemia in an uremic subject. N Engl J Med 280:240-244, 1969

16. Benesch R, Benesch RE: Intracellular organic phosphates as regulators of oxygen release by hemoglobin. Biochem Biophys Res Commun 26:162, 1967

17. Jacob HS, Amsden P: Acute hemolytic anemia with rigid red cells in hypophosphatemia. N Engl J Med 285:1446, 1971

18. Travis SF, Sugerman HJ, Ruberg RL, et al: Alterations of red cell glycolytic intermediates and oxygen transport as a consequence of hypophosphatemia in patients receiving intravenous hyperalimentation. N Engl J Med 285:763-768, 1971

19. Klock JC, Williams HE, Mentzer WC: Hemolytic anemia and somatic cell dysfunction in severe hypophosphatemia. Arch Intern Med 134:360-364, 1974

20. Fuller TJ, Nichols WW, Brenner BJ, et al: Reversible depression in myocardial performance in dogs with experimental phosphorus deficiency. J Clin Invest 62:1194, 1978

21. O'Connor LR, Klein KL, Bethune JE: Effect of hypophosphatemia on myocardial performance in man. N Engl J Med 297: 901, Sep 29, 1977

22. Darsee JR, Nutter DO: Reversible severe congestive cardiomyopathy in three cases of hypophosphatemia. Ann Intern Med 89:867-870, 1978

23. Darsee JR: Hypophosphatemic myocardial dysfunction: The role of phosphorus and high-energy phosphate compounds in myocardial function and dysfunction, *In* Hurst JW (Ed): Update III—"The Heart." New York, McGraw-Hill Book Co, 1979, pp 1-8

24. Craddock PR, Yawata Y, Van Santen L, et al: Acquired phagocyte dysfunction: A complication of the hypophosphatemia of parenteral hyperalimentation. N Engl J Med 290:1403, 1974

25. Mollison PL: Observations on cases of starvation at Belsen. Br Med J 1:4-8, 1946

26. Garner GB, Heubner PF, O'Dell BL: Dietary phosphorus and salmonellosis in guinea pigs. Fed Proc 26:799, 1967

27. Lichtman MA: Hypoalimentation during hyperalimentation. N Engl J Med 290:1432-1433, 1974

28. Yawata Y, Hebbel RP, Silvis S, et al: Blood cell abnormalities complicating the hypophosphatemia of hyperalimentation: Erythrocytes and platelet ATP deficiency associated with hemolytic anemia and bleeding in hyperalimented dogs. J Lab Clin Med 84:643-653, 1974

29. Silvis SE, Pargas PD: Paresthesias, weakness, seizures and hypophosphatemia in patients receiving hyperalimentation. Gastroenterology 62:513-520, 1972

30. Gold LW, Massry GS, Arieff AI, et al: Renal bicarbonate wasting during phosphate depletion: A possible cause of altered acid base homeostasis in hyperthyroidism. J Clin Invest 52:2556-2562, 1973

31. Emmett M, Goldfarb S, Agus ZS, et al: The pathophysiology of acid-base changes in chronically phosphate-depleted rats. J Clin Invest 59:291-298, 1977

32. Giammarco R, Goldstein MB, Halperin ML, et al: Renal tubular acidosis during therapy for diabetic ketoacidosis. Can Med Assoc J 112:463-466, 1975

33. Steele TH: Impaired bicarbonate reabsorption in the phosphate-depleted rat. Mineral Electrolyte Metab 2:74-80, 1979

34. Schmidt RW: Effects of phosphate depletion on acid-base status in dogs. Metabolism 27:943-952, 1978

35. Cooke N, Teitelbaum S, Avioli LV: Antacid-induced osteomalacia and nephrolithiasis. Arch Intern Med 138:1007-1009, 1978

36. Dominguez JH, Gray RW, Lemann J Jr: Dietary phosphate deprivation in women and men: Effects on mineral and acid-balances, parathyroid hormone and the metabolism of 25 -OH-Vitamin D. J Clin Endocin Metab 43:1056-1068, 1976

37. Weintraub MI: Hypophosphatemia mimicking acute Guillain-Barre-Strohl syndrome. JAMA 235:1040-1041, 1976

38. Newman JH, Neff TA, Ziporin P: Acute respiratory failure associated with hypophosphatemia. N Engl J Med 296:1101-1103, 1976

39. Frank BW, Kern F Jr: Serum inorganic phosphorus during hepatic coma. Arch Intern Med 110:865-871, 1962

40. Miller PD, Heinig RE, Waterhouse C: Treatment of alcoholic acidosis. Arch Intern Med 138:67-72, 1978

41. Farber E: ATP and cell integrity. Fed Proc 32:1534-1539, 1973

42. Lehninger AL: The biochemistry of muscle and motile systems, chap 27, *In* Biochemistry, 2nd Ed. New York, Worth Pub, 1975, p 768

43. Veech RL, Lawson WR, Cornell NW, et al: Cytosolic phosphoryation potential. J Biol Chemist 254:6538-6547, 1979

44. Erecinska M, Stubbs M, Miyaa Y, et al: Regulation of cellular metabolism by intracellular phosphate. Biochim Biophys Acta 462:20-35, 1977

45. Sestocft L: Regulatory processes in rat liver induced by sudden changes in fructose concentration, *In* Lundquist F, Tygstrup N (Eds): Regulation of Hepatic Metabolism. Copenhagen, Munksgaard, 1974, pp 285-301

46. Morris RC, Brewer ED, Brater C: Evidence of a severe phosphate-depletion disturbance of cellular metabolism in patients with hereditary fructose intolerance (HPT). Clin Res 28:556A, 1980

47. Morris RC, Nigon K, Reed EB: Evidence that the severity of depletion of inorganic phosphate determines the severity of the disturbance of adenine nucleotide metabolism in the liver and renal cortex of the fructose-loaded rat. J Clin Invest 61:209-220, 1978

48. Knochel JP, Haller R, Ferguson E: Selective phosphorus deficiency in the hyperalimented dog and phosphorylation potentials in the muscle cell. *In* Massry SG, Ritz E, Jahn H (Eds): Phosphate and Minerals in Health and Disease. New York, Plenum Press, 1980, pp 323-335

49. Friedländer K, Rosenthal WG: Uber der einfluss Phosphorsaureions auf den Blut und Harnzucker des normalgen und des diabetischen Organismus. Arch Exp Path Pharmakol 112:66-81, 1926

50. Franks M, Berris RF, Kaplan NO, et al: Metabolic studies in diabetic acidosis: II. The effect of the administration of sodium phosphate. Arch Intern Med 81:42-55, 1948

51. Kohaut EC, Klish WJ, Beachler CW, et al: Reduced renal acid excretion in malnutrition: A result of phosphate depletion. Am J Clin Nutr 30:861-867, 1977

52. Lentz RD, Brown DM, Kjellstrand CM: Treatment of severe hypophosphatemia. Ann Intern Med 89:941-944, 1978

53. Zipf WB, Bacon GE, Spencer ML, et al: Hypocalcemia, hypomagnesemia, and transient hypoparathyroidism during therapy with potassium phosphate in diabetic ketoacidosis. Diabetes Care 2:265-268, 1979

54. Winter RJ, Harris CJ, Phillips LS, et al: Diabetic ketoacidosis induction of hypocalcema and hypomagnesemia by phosphate therapy. Am J Med 67:897-900, 1979

55. Hebert LA, Lemann J, Peterson JR, et al: Studies of the mechanism by which phosphate infusion lowers serum calcium concentration. J Clin Invest 45:1886, 1966

56. Anast S, Winnacker JL, Forte LR, et al: Impaired release of parathyroid hormone in magnesium deficiency. J Clin Endocrinol Metab 42:707, 1976

57. Martin HE, Smith K, Wilson ML: The fluid and electrolyte therapy of severe diabetic acidosis and ketosis. Am J Med 24: 376-389, 1958

Clinicopathologic Conference

Discussants

DAVID J. CAMPISI, MD
CHARLES R. McELROY, MD
J. MICHAEL CRILEY, MD
FREDRICK GILKEY, MD

Editors

DAVID J. CAMPISI, MD
JOHN L. SHERMAN, MD

From the Department of Medicine, UCLA School of Medicine, Center for the Health Sciences, Los Angeles

Refer to: Campisi DJ, McElroy CR, Criley JM, et al: Jaundice, hepatosplenomegaly and liver failure in a 60-year-old woman, UCLA School of Medicine (Clinicopathologic Conference). West J Med 134:27-33, Jan 1981

Jaundice, Hepatosplenomegaly and Liver Failure in a 60-Year-Old Woman

Report of the Case

DAVID J. CAMPISI, MD:* The patient is a 60-year-old white woman admitted because of increasing abdominal girth and abdominal pain. She first noted intermittent scleral icterus approximately ten years before the current admission, but did not seek medical care. Five years before admission she experienced increasing abdominal girth and leg edema and was treated with furosemide (Lasix), with some relief of symptoms.

Four years before admission she was admitted to another hospital where a vagotomy and a pyloroplasty were carried out for upper gastrointestinal hemorrhage. At that time ascites was present, and an intraoperative liver biopsy showed nonspecific periportal inflammation without fibrosis. She was able to continue her work in a dry-cleaning plant after her discharge from the hospital.

She was readmitted to the same hospital two years before her present admission for further evaluation of ascites and edema. The physical examination at that time showed no spider angiomata. The liver edge was firm and slightly tender, and was palpable 5 cm below the costal margin. The spleen was also palpable. Ascites was present. The prothrombin time was 37 percent and was only partially corrected with parenteral administration of vitamin K. The bilirubin was 1.4 mg per dl, alkaline phosphatase 41 King-Armstrong units, SGOT (serum glutamic oxaloacetic transaminase, now known as serum aspartate aminotransferase) 75. Bromsulfophthalein (BSP) retention was 31 percent at 45 minutes. An x-ray study of the chest showed borderline cardiomegaly without intracardiac calcifications. An intravenous cholangiogram showed no evidence of obstruction. The liver scan showed diminished uptake with splenomegaly. Results of a percutaneous liver biopsy were interpreted as showing chronic active hepatitis. She was discharged on a regimen of prednisone and aldactazide.

Her abdominal girth was stable until eight months before the present admission, when she noted increasing girth and abdominal discomfort. She had intermittent temperature elevations to 39°C (102.2°F) which did not respond to orally given antibiotics. She was admitted to this hospital.

She had had a single episode of rheumatic fever at age 15 but no residual cardiac symptoms. She had worked in a dry-cleaning plant for more than 20 years and was exposed to a variety of solvents including carbon tetrachloride. She said she did not use alcohol, tobacco or drugs.

On examination the patient was very jaundiced and seemed slightly confused. Pulse was 110 beats per minute and regular, blood pressure 120/80 mm of mercury, respirations 16 per minute and temperature 38.4°C (101.1°F). The neck veins were distended to the angle of the jaw at 30 de-

*Assistant Professor of Medicine.

Reprint requests to: David J. Campisi, MD, 1360 West Sixth Street, San Pedro, CA 90732.

grees, the lungs were clear. There was a regular rhythm with a prominent S_4 gallop sound. The abdomen was distended; frank ascites was present. The liver was barely palpable at the costal margin; there was 2 plus pitting edema of the lower extremities.

Laboratory studies gave the following values: hemoglobin 12 grams per dl, leukocyte count 18,200 (88 percent segmented cells, 3 percent band cells, 3 percent lymphocytes, 6 percent monocytes), erythrocyte sedimentation rate 22, platelets 30,000. Other findings were as follows: electrolytes normal, blood urea nitrogen 25 mg per dl, creatinine 1.1 mg per dl, total bilirubin 12.2 mg per dl, alkaline phosphatase 370 units per dl, lactic dehydrogenase (LD) 330 units, SGOT 74 units, total protein 7 grams per dl, albumin 2.6 grams per dl. Findings on analysis of urine showed the presence of bile but were otherwise normal. Antinuclear antibody and HB_sAg studies were negative. An electrocardiogram showed low voltage in the limb leads. An x-ray study of the chest showed cardiomegaly, elevated diaphragms with a small free left-sided pleural effusion, and discoid atelectasis at right base.

An upper gastrointestinal series showed probable esophageal varices and ascites. There was pronounced osteoporosis with multiple vertebral compression fractures. On a liver scan there was decreased uptake in a patchy pattern with increased uptake in spleen and bone marrow consistent with cirrhosis. A bone marrow aspirate found adequate megakaryocytes and hyperplasia of erythroid series.

Paracentesis yielded icteric fluid with 11,250 erythrocytes, 70 leukocytes, protein value of 1.0 grams, LD value of 100 and glucose level of 115 mg per dl. Cultures were negative for bacteria and acid-fast bacilli.

Thoracentesis yielded 700 ml of icteric blood-tinged fluid with 8,200 erythrocytes, 210 leukocytes (38 percent lymphocytes, 9 percent polymorphonuclear cells and 53 percent mesothelial cells), protein 1.8 grams, glucose 138 mg. Culture for bacteria and acid-fast bacilli showed no growth. Blood cultures also showed no growth.

The patient was given bedrest and begun on a regimen of spironolactone, fluid restriction, protein restriction and orally given neomycin. On the ninth hospital day the patient became acutely short of breath and complained of pleuritic right middle chest pain. There was increased intensity of the second heart sound with a new right lateral pleural friction rub heard. On an x-ray film of the chest a new pleural-based density in right middle chest was noted. Arterial blood gases on room air showed an oxygen pressure (Po_2) of 68 mm of mercury, a carbon dioxide pressure (Pco_2) of 36 mm of mercury and a pH of 7.46.

Nasal administration of oxygen was begun and the patient's dyspnea improved. Review of the liver biopsy results from two years previously showed no evidence of chronic active hepatitis, but no specific diagnosis could be made.

After a thoracentesis, the patient's dyspnea improved but the fluid reaccumulated 24 hours later. A diagnostic procedure was carried out on the 20th hospital day.

CHARLES R. MCELROY, MD:* The patient is a 60-year-old woman with an illness of greater than ten years duration which had a variety of manifestations including jaundice, hepatosplenomegaly, ascites, peripheral edema, hepatic insufficiency and, presumably, esophageal varices at the end of the course. She had temperatures as high as 39°C (102.2°F) during the year before her final hospital admission. Hematologic problems included persistent anemia, significant thrombocytopenia with a brisk leukocytosis toward the end. In addition, she had florid hyperglobulinemia with hypoalbuminemia, which may in part be responsible for the ascites and pleural effusion. During the final hospital course she appeared to have suffered a pulmonary embolism. An electrocardiogram indicated cardiomegaly with low voltage in the limb leads.

The patient presented initially with jaundice, abdominal swelling and peripheral edema. Apparently there were no other significant symptoms. Berner, Fred, Riggs and Davis studied a large number of cases with this presentation.[1] Of the patients, 75 percent were found to have typical hepatic cirrhosis and 30 percent a malignant condition of one variety or another. Not too surprisingly, males have a predominance of hepatoma while females were more likely to have an ovarian carcinoma. Interestingly, in their series, tuberculous peritonitis was present in only 2 percent. Two patients had aortic stenosis, with essentially no symptoms relevant to the cardiovascular system. Hyman and colleagues[2] found a similar distribution of causes with the exception that far more of their patients had tuberculous peritonitis. A variety of other unusual entities have been the sub-

*Associate Professor of Medicine and Director, Emergency Medicine Center, UCLA Center for the Health Sciences.

jects of single case reports: Meig syndrome, myxedema, Budd-Chiari syndrome, inferior vena cava obstruction, peritoneal sarcoid and chronic pancreatitis.[4-7] Additionally, endomyocardial fibroelastosis (which is reported quite widely in Africa and the Far East), chronic constrictive pericarditis[8] and atrial myxoma have all been reported to have a presentation like that in the case we are discussing.

Four years before the patient's final admission a peptic ulcer developed; a vagotomy and pyloroplasty were done. Ascites was present at that time. An intraoperative liver biopsy showed only nonspecific periportal inflammation without much fibrosis. An abdominal tumor should have been apparent to the surgeon at the time of operation, either as peritoneal studding causing the ascites or as a mass causing obstructive liver disease. Therefore, I do not think that those diagnoses are tenable. A nonspecific biopsy finding makes cirrhosis much less likely. Tuberculous peritonitis can be a very difficult diagnosis to make and can masquerade as a variety of entities. This patient presumably did not have peritoneal or omental implants but this does not entirely rule tuberculosis out. We are not given the results of a purified protein derivative skin test or any other evidence to support the diagnosis of tuberculosis. In addition, it seems unlikely that jaundice would be a result of tuberculosis when there were nonspecific liver biopsy findings, unless underlying Gilbert disease was present.

Primary biliary cirrhosis (PBC), or so-called nonsuppurative chronic destructive cholangitis, seemed to be an appealing diagnosis in this case, but is too obvious a cause to be found in a CPC. The patient is a woman of the right age, presenting in cryptic fashion. A needle biopsy of the liver is often not helpful, and results may be reported as chronic active hepatitis.[8] In support of this diagnosis are the following: the pattern of liver enzyme abnormalities (high alkaline phosphatase with only minimal elevations of the transaminases); the presence of peptic ulcer disease as a complication; elevation of serum globulins, primarily of the IgM fraction, and progressive hypoalbuminemia.[10] However, there are a number of problems in hypothesizing this diagnosis. First, given the paucity of fibrosis shown on biopsy findings, why should she have been jaundiced? I could explain this by the coexistence of Gilbert disease. Second, why would she have ascites and peripheral edema if she had not progressed to the precirrhotic stage of the disease. Finally, primary biliary cirrhosis most commonly presents as persistent pruritis and fatigue, with physical findings of excoriations and hyperpigmentation, which were not described in this patient. But Sherlock and others have reported cases of patients who have only ascites and peripheral edema as the first manifestation of their primary biliary cirrhosis and are without fever, fatigue or pruritis.[10-12] So an atypical presentation of primary biliary cirrhosis is a possibility.

Two years before her final admission she was again admitted to hospital for evaluation of edema and ascites. An intravenous cholangiogram (IVC) showed no evidence for obstruction, which confirmed the surgeon's observation of two years before. A liver scan showed decreased uptake and hepatosplenomegaly and a percutaneous liver biopsy was read as showing chronic active hepatitis. She again had a notably elevated alkaline phosphatase value with lesser elevations in transaminases. Hepatic dysfunction was shown with pronounced BSP retention and prolonged prothrombin time. She was treated with prednisone for a diagnosis of chronic active hepatitis. At that point cardiomegaly was reported for the first time and, significantly, we are told there were no intracardiac calcifications.

A diagnosis of primary biliary cirrhosis is at odds with the findings on the IVC and cannot explain the cardiomegaly. The absence of cardiac calcifications and of specific cardiac symptoms make a diagnosis of rheumatic valvular disease less likely.

Eight months before admission here, an abrupt increase in her abdominal girth occurred and temperature elevations to 39°C (102.2°F) were noted for the first time. These led to her admission here. Several important clues were found during this hospital stay. Temperatures to 38.4°C (101.1°F) were documented in the hospital. She was noted to have distended neck veins, an S_4 gallop with no other auscultatory abnormalities and low voltage in the limb leads of an electrocardiogram. In addition, she had anemia, pronounced thrombocytopenia but significant leukocytosis. A bone marrow examination showed erythroid hyperplasia and adequate megakaryocytes, which indicates peripheral destruction of these blood elements. The bilirubin and alkaline phosphatase values were notably elevated out of proportion to the increases in other liver enzymes. Findings on an upper gastrointestinal series were compatible with esophageal varices and osteopenia.

Many of these findings could be explained by a diagnosis of primary biliary cirrhosis. Patients with that disease may be anemic from peptic ulcer disease. They may have malabsorption of calcium and, consequently, diffuse osteopenia and fractures. Their conditions may progress to end-stage cirrhosis with varices and death from liver failure may occur. But there are several findings which lead me away from that diagnosis. First, it is not common for patients with primary biliary cirrhosis to have recurrent fevers of this magnitude. I would have to postulate the development of a hepatoma complicating cirrhosis to explain the fever and sudden worsening of the ascites. Second, primary biliary cirrhosis would not explain the cardiomegaly and the low voltage in the limb leads of the electrocardiogram. Third, it would not account for the apparent pulmonary embolism that occurred during the hospital stay. Specifically I must explain why a patient with prolonged partial thromboplastin time and thrombocytopenia would have a pulmonary embolism. One possibility is venous obstruction due to a hepatoma, which produced stasis and thrombosis leading to pulmonary embolism. Another possibility is that the embolus was not composed of a thrombus but consisted of tumor. This last consideration led me to the diagnosis that I am going to make.

I will exclude primary biliary cirrhosis with subsequent evolution to hepatoma for the reasons stated above. Tuberculous peritonitis seems unlikely because of the negative findings at laparotomy and the character of the ascitic and pleural fluids. The pleural fluid was a blood-tinged transudate which points towards a tumor or heart failure more than to tuberculosis.[13]

Chronic constrictive pericarditis due to old tuberculosis could explain most of this patient's condition. But more than 70 percent of patients with this condition will have calcifications in the pericardium, which were not seen in this patient.[14] The recent fevers could be due to reactivation of the underlying tuberculosis. But this cannot explain the apparent pulmonary embolism.

Finally, I would like to turn to intracavitary disease of the heart. Atrial myxomas, like tuberculosis and syphilis, are notorious for their cryptic presentations. They may mimic rheumatic heart disease, tuberculosis, constrictive pericarditis, cirrhosis, heart failure and systemic lupus erythematosus, among others.

I am going to propose that a myxoma began its slow growth in this patient's right atrium many years before the onset of her symptoms. It gradually filled the cavity and obstructed filling of the right atrium, causing chronic passive congestion of the liver, progressive cirrhosis, ascites and edema. There are several case reports[15-18] of patients with right atrial myxomas presenting in just this manner.

The absence of a murmur in this patient is not surprising. In a series reported by Symbas and co-workers,[17] 25 percent of the patients with right atrial myxomas had no murmurs. Myxomas may be fixed to the atrial septum so that they are not very mobile. In these instances they can grow to be remarkably large and can cause problems by obstruction of right-sided filling rather than by a ball valve mechanism.

Thrombocytopenia has been reported to occur in myxoma by a variety of mechanisms.[19] There may be immunologic destruction of platelets or splenic sequestration as a result of chronic portal hypertension. In addition the "Waring blender" effect—mechanical trauma to platelets and red cells—has been shown to be a cause of both anemia and thrombocytopenia with myxomas.

The anemia seen in myxomas may represent the anemia of chronic disease or may be due to mechanical or immunologic hemolysis. Interestingly, 10 percent to 15 percent of patients with right atrial myxomas will present with polycythemia. Usually this is seen in patients with a patent foramen ovale and right-to-left shunts leading to hypoxemia.[20]

Leukocytosis and broad-based elevations in immune globulins are commonly seen.[21] The exact mechanism is not clear but seems to be related to frequent embolization of fragments of gelatinous tumor to various capillary beds that induce inflammatory and immunologic reactions.

Hepatic abnormalities have been frequently reported in association with atrial myxomas.[21] The pattern of enzyme elevations is similar to that seen in this case: elevation of alkaline phosphatase out of proportion to the transaminases. The jaundice and hypoalbuminemia are the results of progessive hepatic fibrosis.

Fever is commonly seen with myxomas and may mimic bacterial endocarditis. Whether the fever is an immune response to the tumor or is the result of recurrent microembolizations is unknown. A wide variety of other systemic complaints have been reported to occur with myxomas, including arthritis, malaise and weight loss.

Cardiomegaly and low voltage electrocardiograms have also been seen with atrial myxomas.

In summary, I believe that this patient had an obstructing right atrial myxoma that caused chronic passive congestion of the liver and cirrhosis. The diagnostic procedure was either an echocardiogram or a right-sided heart catheterization.

J. MICHAEL CRILEY, MD:* Because this woman was admitted with liver disease and a history of chronic exposure to solvents, her physicians focused on this aspect of her illness during the initial phase of her hospital stay. However, when the liver biopsy slides were obtained and reviewed, they did not confirm chronic active hepatitis but instead showed central vein dilatation. The gastroenterology staff, after reviewing the slides, suggested the possible diagnosis of constrictive pericarditis.

Accordingly, a cardiac consultation was obtained, and the following features were noted. There was elevation of the neck veins at 30 degrees, a paradoxical pulse of 20 mm of mercury and an S_3 gallop sound. The electrocardiogram was repeated at double standard (1 mv = 20 mm) because of the extreme low voltage and showed disproportionately large P waves, and the sum of the QRS voltages in leads I, II and III was less than 0.6 mV, with an indeterminate frontal plane axis with nonspecific T wave changes. An echocardiogram was taken with considerable technical difficulty; normal left heart chamber size on the left side and a small to moderate pericardial effusion were shown.

A right-sided heart catheterization was carried out with a flotation catheter, which showed unusual pressure contours (Figure 1). The right atrial pressure was greatly elevated, with prominent *a* waves of 27 mm of mercury which were taller than the right ventricular or pulmonary artery systolic pressures. When the atrial and ventricular pressures were superimposed (Figure 2), a 10 mm of mercury diastolic gradient was noted. The atrial pressures exhibited a prominent initial *y* descent followed by the large *a* wave under which most of the gradient was manifest.

A manual injection of contrast medium in the right atrium was done to determine the size of the pericardial effusion. It was found to be of moderate size. There was no distortion of the lateral right atrial wall to suggest constriction. The cardiac output was only 1.8 liters per minute, and the pulmonary vascular resistance was elevated to 7 Wood units (560 dynes-secs cm^{-5}).

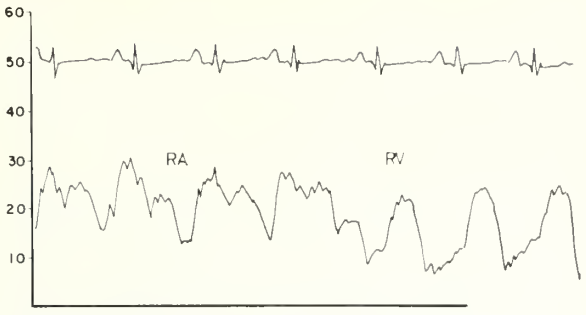


Figure 1.—Right-sided heart catheterization pressure tracing. Top of figure represents simultaneous electrocardiogram. Bottom tracing is continuous pressure measurement. RA = right atrial pressure. RV = right ventricular pressure.

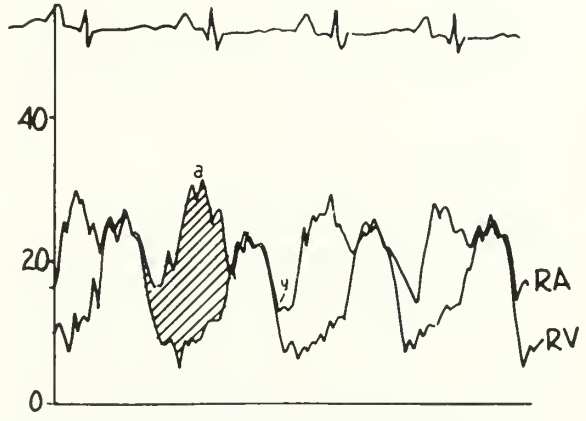


Figure 2.—Superimposed right atrial and right ventricular pressure tracings showing a 10 mm diastolic gradient.

On later review of the pressure data, an explanation for the pressure gradient across the tricuspid valve was sought and the possibility of a localized constricting band or pericardial cyst was considered. However, on review of the manual injection right atriogram, a possible filling defect was noted in the right atrium during systole only. Therefore, the diagnosis of a right atrial myxoma, tumor or thrombus was considered. Serial film angiograms (Figure 3) confirmed the presence of a mobile, large filling defect, which occupied most of a greatly enlarged right atrium during systole, and the entire inflow of the small right ventricle during diastole. No filling defects were seen in the left atrium on the levogram.

Although the diagnosis of a potentially curable right atrial myxoma was thus seemingly confirmed, the precarious hepatic, pulmonary and hemo-

*Professor of Medicine, and Chief, Division of Cardiology, LAC-Harbor-UCLA Medical Center, Torrance.

static function rendered the patient an extremely high operative risk. She was operated upon and found to have a greatly dilated right atrium almost completely filled by a gelatinous red tumor which was attached by a narrow pedicle to the atrial septum. The tricuspid valve had been traumatized by repeated impact from the tumor, but it was elected not to replace it because of the patient's poor condition. Her postoperative course was a constant struggle with arrhythmias and fluctuating pulmonary and hepatic failure, and the patient died on the 26th postoperative day.

Figure 3.—Right-sided heart angiogram. **Top panel:** systole showing a large filling defect in the right atrium. **Bottom panel:** diastole filling defect moves into right ventricular inflow tract.

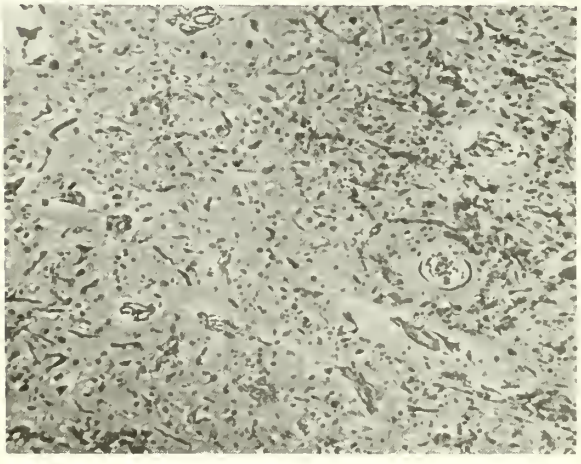


Figure 4.—Low-power view of atrial myxoma. (Hematoxylin-eosin stain, original ×140).

FREDRICK GILKEY, MD:* Surgical operation was carried out five weeks after admission, at which time a 110-gram, 8 by 6 by 5 cm tumor was removed from the right atrium. It was pedunculated and consisted of friable, gelatinous material, ranging from red to tan.

Histologically, the tumor was of low cellularity (Figure 4). The polygonal cells were scattered singly, in clusters and in strands within a loose, granular to homogeneous, eosinophilic stroma. There was prominent perivascular cuffing by tumor cells, which at times seemed to replace the endothelium lining the vessels (Figure 5). The stroma was alcian-blue positive, indicating the presence of acid mucopolysaccharides (connective tissue mucin). Hemorrhage, recent and remote, was evident.

These are typical findings of the cardiac myxoma,[22] a tumor that is easier to diagnose under the microscope than clinically. It can present as valvular obstruction; pulmonary, peripheral or central nervous system vascular obstruction, or liver disease as in this patient. It can mimic bacterial endocarditis, be found incidentally at autopsy or can be noted during cardiac operations[22-25]

*Assistant Professor of Pathology.

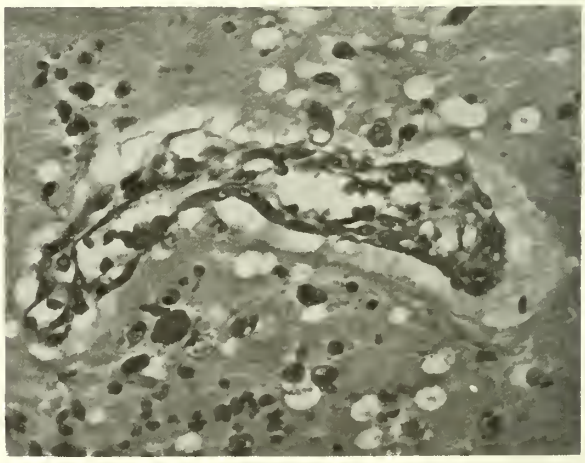


Figure 5.—High power view of myxoma. Investment of blood vessel by tumor cells which are difficult to distinguish from endothelial cells. (Hematoxylin-eosin stain, original ×440).

(Table 1). Most are located in the left atrium and they are found only rarely in the ventricles (Table 2).

Myxoma is the most common neoplasm arising in the heart.[22] While the earlier contention that myxomas represented organized thrombi has generally been abandoned,[22-24] determination of the cell of origin is more difficult. Proposed progenitors include multipotential subendocardial mesenchymal cells,[22-24] subendocardial reserve cells,[26] the endothelium itself[24] and even that two distinct neoplasms are involved—that is, a true endothelioma and a myofibroma.[27] That multipotential cells are the source is supported by the ultrastructural finding of differentiation toward fibrocytes, smooth muscle and endothelial cells in the same tumor, as well as primitive, unclassifiable cells.[23]

The patient died after a one-month postoperative course characterized by adult respiratory distress syndrome and hepatorenal failure. On autopsy there were findings of diffuse alveolar damage.[28] The heart had changes related to surgical operation, but no residual tumor. There was, however, a tumor embolus in a pulmonary artery. The shrunken (750 grams) liver had micronodular and macronodular cirrhosis. The histologic pattern was "reversed lobulation," with fibrous bands joining central veins, leaving regenerative nodules centering on the portal tracts. This constitutes cardiac cirrhosis. There was no evidence of hepatitis.

The final anatomic diagnosis was as follows: right atrial myxoma, with tumor embolus to lung; cardiac cirrhosis of liver from chronic passive congestion.

TABLE 1.—*Cardiac Myxoma: Clinical Presentation in 130 Patients**†*

Signs and symptoms of mitral valve disease	57
Embolic phenomena	36
No cardiac symptoms—incidental finding	16
Signs and symptoms of tricuspid valve disease	6
Sudden unexpected death	5
Pericarditis	4
Myocardial infarction	3
Signs and symptoms of pulmonary valve disease	2
Fever of undetermined origin	2

*One patient with multiple myxomas had signs and symptoms of mitral and tricuspid valve disease.

†Reprinted with permission from Armed Forces Institute of Pathology.[22(p5)]

TABLE 2.—*Cardiac Myxoma: Location of 138 Myxomas in 130 Patients**†*

Site	*Number*	*Percent*
Left atrium	103	74.5
Right atrium	25	18.1
Right ventricle	5	3.7
Left ventricle	5	3.7

*Multiple myxomas were present in six patients.

†Reprinted with permission from Armed Forces Institute of Pathology.[22(p7)]

REFERENCES

1. Berner C, Fred HL, Riggs S, et al: Diagnostic probabilities in patients with conspicuous ascites. Arch Intern Med 113:687-690, May 1964

2. Hyman S, Villa F, Steigmann S: Mimetic aspects of ascites. JAMA 183:651-655, Feb 23, 1963

3. Meigs JB, Cass JW: Fibroma of the ovaries with ascites of the hydrothorax: Report of seven cases. Am J Obstet Gynecol 33:249-267, 1937

4. Kocen RS, Atkinson M: Ascites in hypothyroidism. Lancet 1:527-530, Mar 1963

5. Baggenstoss AH, Wollaeger EE: Portal hypertension due to chronic occlusion of the extra-hepatic portion of the portal vein: Its relation to ascites. Am J Med 21:16-25, Jul 1956

6. Wong M, Rosen SW: Ascites and sarcoidosis due to peritoneal involvement. Ann Intern Med 57:277-280, Aug 1962

7. Barua RL, Villa S. Steigmann F: Massive ascites due to pancreatitis. Am J Digest Dis 7:900-906, Oct 1962

8. Hill RW, Foulk T, Butt HR, et al: Chronic constrictive pericarditis simulating primary hepatic disease. Proc Mayo Clinic 31:627-631, Nov 28, 1956

9. Popper H: The problem of histologic evaluation of primary biliary cirrhosis. Virchow's Archiv [Pathol Anat] 379:99-102, 1979

10. Sherlock S: Primary biliary cirrhosis. Mt Sinai J Med 44: 6:790-797, Nov-Dec 1977

11. Sherlock S: Primary biliary cirrhosis. Am J Med 65:2, Aug 1978

12. Long RG, Scheuer TL, Sherlock S: Presentation and course of asymptomatic primary biliary cirrhosis. Gastroenterology 72: 1204-1207, 1977

13. Rovelstad RA, Bartholomew L, Kane JC: Helpful laboratory procedures in the differential diagnosis of ascites. Proc Mayo Clinic 34:565-568, 1959

14. Hageman JC, D'Esopo N, Glenn W: Tuberculosis of the pericardium: A long-term analysis of 44 proven cases. N Engl J Med 270:7:327-332, Feb 13, 1964

15. Emanuel RW, Lloyd WE: Case reports: Right atrial myxoma mistaken for constrictive pericarditis. Br Heart J 24:796-800, 1964

16. Peters MD, Hall RJ, Cooley MA, et al: The clinical syndrome of atrial myxoma. JAMA 230:5:695-700, Nov 4, 1974

17. Symbas P, Abbott O, Logan WD, et al: Myxomas: Special emphasis on unusual manifestations. Chest 59:504-510, 1974

18. Wilman VL, Symbas P, Mamiya RT, et al: Unusual aspects of intracavitary tumors of the heart: Report of two cases. Dis Chest 47:699, 1965

19. Vuopio P, Nikkila E: Hemolytic anemia and thrombocytopenia in a case of left atrial myxoma associated with mitral stenosis. Am J Cardiol 17:585-589, 1966

20. Morrissey JF, Campeti FL, Mahoney EB, et al: Right atrial myxoma: Report of two cases and a review of the literature. Am Heart J 66:4-14, 1963

21. Kluge TH, Ulal SR, Gerbode F: Dysfunction of the liver in cardiac myxoma. Surg Gynecol Obstet 134:1-3:288-290, 1972

22. McAllister HA Jr, Fenoglio JJ Jr: Tumors of the Cardiovascular System. Washington, DC, Armed Forces Institute of Pathology, 1978, pp 5-20

23. Ferrans VJ, Roberts WC: Structural features of cardiac myxomas. Hum Pathol 4:111-143, 1973

24. Symbas PN, Hatcher CR, Gravanis MB: Myxoma of the heart: Clinical and experimental observations. Ann Surg 183:470-475, 1978

25. Yufe R, Karpati F, Carpenter S: Cardiac myxoma: A diagnostic challenge for the neurologist. Neurology 26:1060-1065, 1976

26. Stein AR, Mauro J, Thibodeau L, et al: The histogenesis of cardiac myxomas: Relation to other proliferative diseases of subendothelial vasoform reserve cells, *In* Sommers S (Ed): Pathology Annual, 1969. New York, Appleton-Century-Crofts, 1969, pp 293-312

27. Mikuz G, Hofstaedter AH, Hager J: Das sogennante Endokard-Myxom. Virchows Arch [Pathol Anat], 380:221-236, 1978

28. Katzenstein A-LA, Bloor CM, Leibow AA: Diffuse alveolar damage: The role of oxygen, shock, and related factors. Am J Pathol 85:210-228, 1976

Refer to: Mahley RW: The role of dietary fat and cholesterol in atherosclerosis and lipoprotein metabolism—Medical Staff Conference, University of California, San Francisco. West J Med 134:34-42, Jan 1981

The Role of Dietary Fat and Cholesterol in Atherosclerosis and Lipoprotein Metabolism

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr, Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR. SMITH:* *The topic of this discussion is the role of dietary fat and cholesterol in atherosclerosis and lipoprotein metabolism. This gives us the opportunity to introduce an important new member of our faculty, Dr. Robert W. Mahley. Dr. Mahley received his medical degree and doctorate from Vanderbilt University. Much of his career has been spent at the National Institutes of Health where most recently he has been head of the Comparative Atherosclerosis and Arterial Metabolism Section in the National Heart, Lung, and Blood Institute. Last fall, Dr. Mahley came to UCSF as Professor of Pathology, with collateral appointment in medicine. Here, he heads an important new institute, the Gladstone Foundation Laboratories for Cardiovascular Disease located at San Francisco General Hospital.*

DR. MAHLEY: In the summer of 1980 the newspapers and popular magazines gave extraordinary coverage to a new national report from the Food and Nutrition Board of the National Academy of Sciences. The study concluded that available research data do not support the link between the consumption of dietary cholesterol and coronary artery heart disease and that there is no need for the average healthy person to restrict consumption of high fat, high cholesterol foods.[1]

The controversy has expanded and the waters have been muddied by claims of an apparent conflict of interest in the association between some of the board members and the food industry. A couple of the scientists are associated with, or have been consultants for, the meat, dairy and egg industries, and a couple of board members are executives of commercial food companies. The public has been confused by this controversy and by the charges of a conflict of interest, and both the public media and people in general are questioning the credibility of the medical and scientific community. The discussion and the debate on the role of dietary fat and cholesterol are not the problem—this is the way of science. The confusion, however, has undermined scientific evaluation in the public's view and this is at least partially because the panel apparently did not consider all the available evidence on the subject.

In my opinion, the panel overstated its conclusions and ignored a large and persuasive body

*Lloyd H. Smith, Jr, MD, Professor and Chairman, Department of Medicine.

ABBREVIATIONS USED IN TEXT

CHD = coronary heart disease
HDL = high-density lipoproteins
HDL_c = cholesterol-induced high-density lipoproteins
HDL_1 = high-density lipoproteins containing E apoprotein
HDL_2 = high-density lipoproteins lacking E apoprotein
LDL = low-density lipoproteins
VLDL = very-low-density lipoproteins

of evidence that shows a clear relationship between plasma cholesterol levels, the intake of dietary fat and cholesterol and accelerated heart disease. When one considers the entire body of data, including epidemiologic and population studies, clinical trials and diet experiments in animals, the evidence overwhelmingly supports the idea that diet and heart disease are strongly linked. I want to review only a few selected data for you.

Epidemiologic and Population Studies

A positive correlation between certain dietary factors and mortality from coronary heart disease (CHD) is evident from various epidemiologic studies. Vital statistics from 30 countries provided by the World Health Organization (WHO) and Food and Agricultural Organization (FAO) of the United Nations indicate that there is a positive correlation between mortality and intake of total calories, total fat, animal fat, meat, cholesterol, eggs and animal protein in men 55 to 59 years of age. There is either no correlation or a negative correlation between coronary heart disease and the intake of vegetable fat, vegetables and fish. As shown in Figure 1, arteriosclerotic and degenerative heart disease are strongly correlated with cholesterol intake. Populations consuming, on the average, more than 500 mg of cholesterol per day (such as in the United States, Australia and Canada) have a death rate per 100,000 male population (aged 55 to 59 years) that is many times greater than that in populations consuming less than 150 mg of cholesterol per day (for example, in Japan).[2]

A positive association between dietary saturated fat and atherosclerotic disease is also clearly shown in other epidemiologic studies. The International Cooperative Study on Epidemiology of Cardiovascular Disease, a prospective study of 40- to 59-year-old men from seven countries, showed that the percentage of total calories

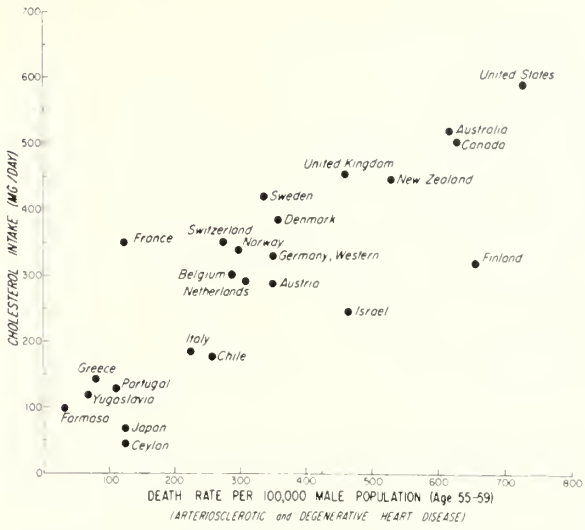


Figure 1.—Death rates from coronary heart disease for the mean of men aged 55 to 59 years in 24 countries significantly correlated with the mean daily intake of cholesterol in the diet. (Reproduced with permission from Connor and Connor.[2])

provided by saturated fatty acids correlates significantly with the incidence of fatal and nonfatal myocardial infarctions. Serum cholesterol levels correlate with both the consumption of saturated fat and the incidence rates.[3] It should be noted that diets high in saturated fats usually contain high levels of cholesterol as well because both occur in similar foods of animal origin.

Population studies link changes in dietary habits with elevations in plasma cholesterol levels and with the occurrence of coronary artery disease. One such study correlates the incidence of coronary artery disease with increased dietary lipid intake and elevated serum cholesterol levels in Japanese men living in Japan or emigrating to the United States (Hawaii or California). Of all the industrialized countries of the world, Japan has one of the lowest rates of coronary heart disease, as shown in Figure 1. This study, begun in 1965, indicates that as Japanese men are assimilated into the westernized society of the United States, they increase their intake of animal products including total fat, saturated fat and cholesterol (Table 1). Associated with the dietary changes, there is an increase in serum cholesterol levels and an increase in CHD. The incidence of deaths due to myocardial infarction and CHD is lowest for native Japanese men and highest for Japanese men living in California.[4]

Changes in diets associated with war-time populations have also provided evidence to support

links between diet and heart disease. During World War II, the invasion and occupation of various Scandinavian countries produced a sharp decline in the consumption of animal fats, eggs and dairy products, and a decline in the death rate from coronary artery disease. In Norway and Finland where shortages of food came early in the war, the decline in CHD also came early. In the Netherlands, however, where the change in eating patterns occurred late in the war, the decline in CHD occurred much later.[5]

Numerous other epidemiologic studies, such as the detailed reviews of Keys[3] and Stamler,[4] give a more complete discussion. However, it is important to point out that such studies do not prove a direct cause and effect relationship between CHD and dietary fats. Like all scientific data, epidemiologic studies must be considered in the light of all available evidence. They do, however, strongly support the diet-lipid-heart disease hypothesis. Atherosclerosis is a complicated disease process upon which we must bring the tools of all disciplines to bear if we are to understand its pathogenesis. Epidemiologic data represent pieces of a very complex puzzle.

Another piece of the puzzle comes from diet studies in animals. These studies appear to have been ignored by the Food and Nutrition Board in their deliberations. Diets high in fat and cholesterol will lead to accelerated atherosclerosis in essentially every animal species that has been studied, and I suggest that humans are no exception.

Animal Studies

One can create dietary and metabolic conditions which will induce, in most animals under study, a form of atherosclerosis that resembles certain aspects of the disease process as it occurs in humans.[6] However, such animal experiments provide us with a slightly different view of the disease than as it occurs in humans. Figure 2 shows a histologically prepared cross section of the anterior descending coronary artery from a cholesterol-fed miniature swine. This animal had had a hypercholesterolemia of 400 mg per dl for about a year. The lumen of the vessel shown in Figure 2 is significantly (60 percent to 70 percent) narrowed by a very typical atheromatous lesion. A characteristic of atherosclerosis in all animal species is the deposition of cholesterol in and around cells of the arterial wall. The cholesterol that accumulates is derived from plasma lipoproteins, and it is important to identify the specific lipoproteins responsible for the delivery of cholesterol to cells and to identify the cell type that accumulates the cholesterol.

It is our contention that animal studies are providing important data that are relevant to humans. They are relevant because they show that high levels of dietary cholesterol change the cholesterol-carrying plasma lipoproteins and that this causes the lipoproteins to deliver cholesterol to the arterial wall. *How the cholesterol is transported and by which lipoproteins may be more important than the absolute level of the plasma cholesterol.* To conclude that a particular dietary regimen (high or low in a specific constituent) is unimportant because it has little or no effect on the total plasma cholesterol, reflects a lack of appreciation of the dynamics of lipoprotein-cholesterol metabolism. The various plasma lipoproteins of humans and animals all transport cholesterol and represent a metabolically diverse group of macromolecules that may have entirely opposite effects on the ingress or egress of cholesterol in the

TABLE 1.—*Dietary Changes Associated With the Emigration of Japanese Men to the United States**

	Japan	*Hawaii*	*California*
Diet			
Total calories	2,164 ±619	2,275 ±736	2,262 ±695
Animal protein (g)	39.8± 22.8	70.5± 32.7	66.0± 24.4
Total fat (g)	36.6± 20.4	85.1± 38.9	94.8± 36.4
Saturated fat (g)	16.0± 13.3	59.1± 32.7	66.3± 30.5
Cholesterol (mg)	464.1±324.4	545.1±316.4	533.2±297.8
Serum cholesterol			
mg/dl	181.1± 38.5	218.3± 38.2	228.2± 42.2
>260 mg/dl (per 1,000)	31.6	124.0	162.5
Myocardial infarction and coronary heart disease deaths			
Incidence compared with Japanese men in Japan	....	Twofold	Threefold

*Modified from Stamler.[4]

arterial wall. An understanding of the diversity of roles of specific lipoprotein classes and subclasses has only begun.

A provocative study by Armstrong and coworkers[7] in monkeys offers an excellent introduction to the value of using animals to study the role of diet in the pathogenesis of atherosclerosis. In this study, rhesus monkeys were fed cholesterol-free or cholesterol-supplemented diets for 18 months. Monkeys fed small amounts of cholesterol had plasma cholesterol levels that were matched with monkeys on the cholesterol-free diet (all monkeys had cholesterol levels of less than 220 mg per dl). At the end of the study, monkeys that received cholesterol in their diets had much more severe atherosclerosis than did the monkeys on the cholesterol-free diet, despite the fact that both groups had the identical plasma cholesterol levels. Adding cholesterol to the diet increased the deposition of cholesterol in the arterial wall without producing an excessive hypercholesterolemia.

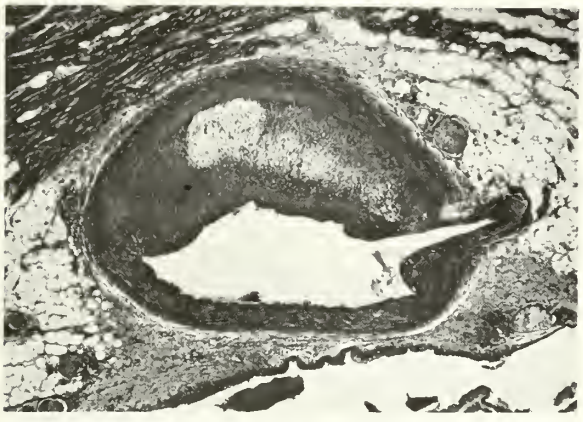


Figure 2.—A cross section of the anterior descending coronary artery from a miniature swine fed a high fat, high cholesterol diet (15 percent lard, 1 percent cholesterol by weight added to a standard chow) for one year. The atherosclerotic lesion has partially occluded the lumen of this major coronary artery.

How did more severe atherosclerois develop in the monkeys consuming the cholesterol-supplemented diet when their plasma cholesterol levels were the same as those of the control (noncholesterol-fed) monkeys? What is the effect of the dietary cholesterol? It is reasonable to speculate that dietary cholesterol (exogenous) is metabolized differently from cholesterol synthesized in the body (endogenous). It is our contention that the intake of dietary cholesterol causes changes in the types and metabolism of plasma lipoproteins, perhaps very subtle changes, or changes that we have not yet identified, but changes, nevertheless, that lead to deposition of cholesterol in tissues.

Changes in Lipoproteins

I wish to describe some of the changes that occur in the lipoproteins after cholesterol feeding and that are associated with accelerated atherosclerosis in nonhuman species of animals. Data

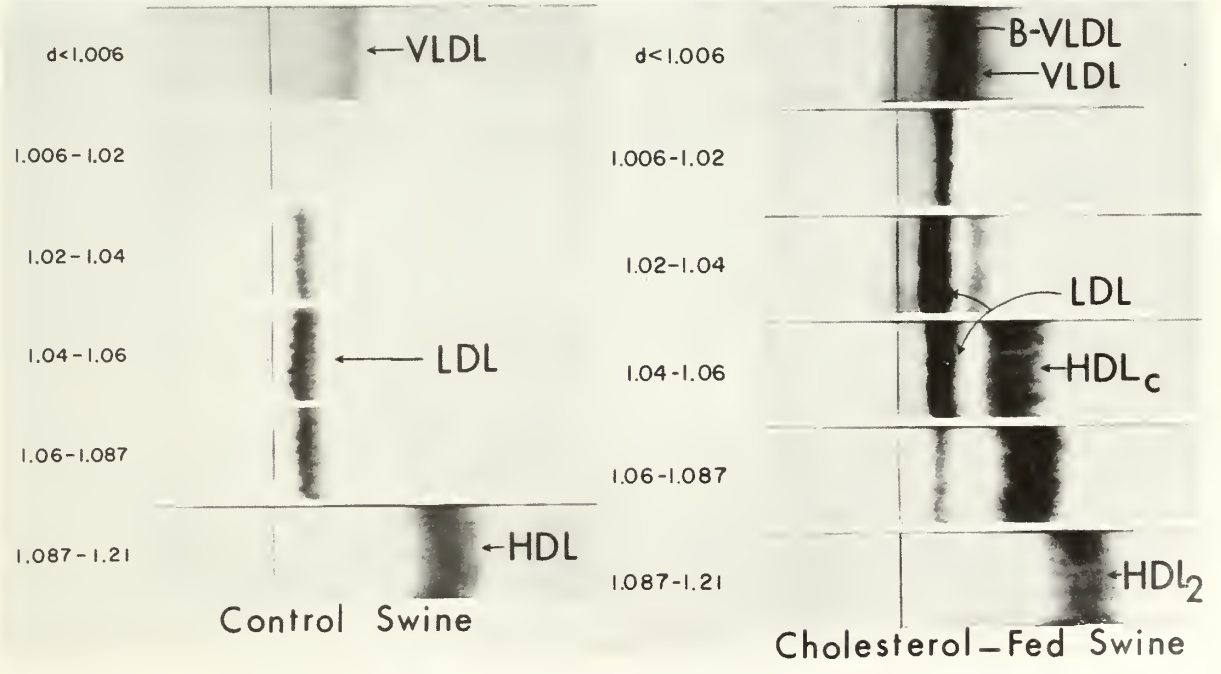


Figure 3.—Comparison of the plasma lipoproteins from a control and a cholesterol-fed miniature swine. (Reproduced with permission from Mahley et al.[9])

show that similar changes in the lipoproteins occur in humans on a high cholesterol diet. Regardless of the species of animal, there are certain consistent changes in the lipoproteins associated with accelerated atherosclerosis induced by the high fat, high cholesterol diets.[3,8]

Figure 3 illustrates the changes that occur by comparing the lipoproteins from a control miniature swine with those from a cholesterol-fed swine. The control swine has lipoproteins very similar to the lipoproteins that occur in humans, including very-low-density lipoproteins (VLDL, or pre-β-lipoproteins), low-density lipoproteins (LDL, or β-lipoproteins) and high-density lipoproteins (HDL, or α-lipoproteins). The atherogenic hyperlipidemia that occurs with cholesterol feeding is characterized by four changes. First, there is the appearance of β-VLDL (or B-VLDL) in the $d<1.006$ ultracentrifugal fraction. The B-VLDL are cholesterol-rich lipoproteins similar to the B-VLDL that occur in patients with type III hyperlipoproteinemia or dysbetalipoproteinemia. Normally, the $d<1.006$ fraction contains only the pre-β-migrating, triglyceride-rich VLDL. The B-VLDL are β-migrating, cholesterol-rich lipoproteins. We have seen this change in every species studied. The second change that occurs with cholesterol feeding is an increase in the LDL, and the third is the appearance of α_2-migrating, cholesterol-rich lipoproteins, referred to as HDL_c. Our data indicate that HDL_c are derived from the typical plasma HDL as they pick up cholesterol from peripheral cells. As the typical HDL become loaded with cholesterol, they increase in size and float at lower densities, becoming the HDL_c. The subscript *c* indicates that the lipoproteins are cholesterol-induced. We believe that the HDL_c transport the cholesterol from peripheral tissues, such as the arterial wall, to the liver for excretion. The presence of a specific protein (the E apoprotein) on the HDL_c serves as the signal for hepatic recognition and uptake.[10,11] By typical HDL, I mean α_1-migrating, small, protein-rich lipoproteins that usually float at a density of 1.063 to 1.21. A fourth change that occurs is a decrease in typical HDL.

In all the species studied, then, there are four changes: (1) the occurrence of B-VLDL, (2) an increase in LDL, (3) the appearance of HDL_c and (4) a decrease in typical HDL.

Interaction of Lipoproteins With Cells

How do these various lipoproteins interact with cells to regulate cholesterol metabolism? The scheme by which various cells metabolize cholesterol is shown in Figure 4. Fibroblasts and smooth muscle cells have on their surfaces specific high-affinity cell surface receptors that recognize the LDL.[12] This recognition of the lipoproteins by the cell receptors starts a series of intracellular events in which the LDL cholesterol is internalized and hydrolyzed, and by which cholesterol metabolism is regulated. Not only do low-density lipoproteins (which contain the B apoprotein) interact with these cell surface receptors, but certain high-den-

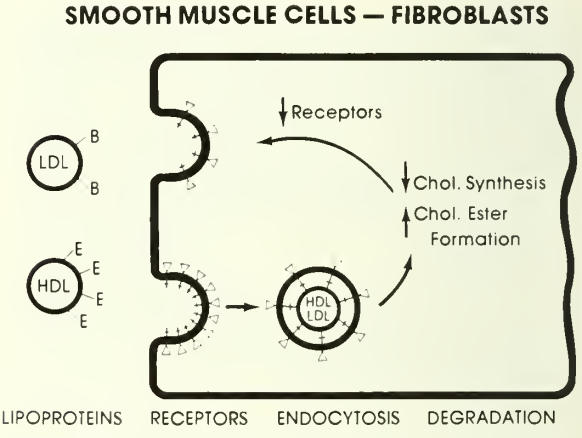


Figure 4.—Schematic diagram illustrating the cell surface receptor binding of the B apoprotein-containing LDL and the E apoprotein-containing HDL. Typical HDL lacking the E apoprotein do not bind. Intracellular cholesterol metabolism is regulated by these lipoproteins. (Chol = cholesterol; HDL = high-density lipoproteins; LDL = low-density lipoproteins.)

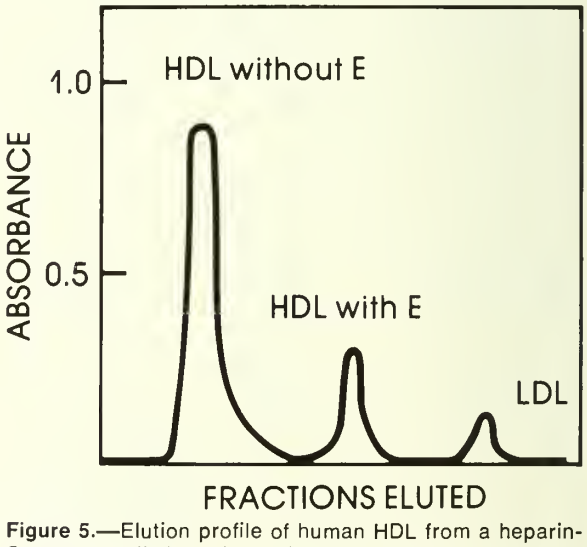


Figure 5.—Elution profile of human HDL from a heparin-Sepharose affinity column. (E = the E apoprotein; HDL = high-density lipoproteins; LDL = low-density lipoproteins.) (See Weisgraber and Mahley[15] for complete description of methodology and for characterization of the subclasses.)

sity lipoproteins (those containing a certain type of protein called the E apoprotein) also interact with the same receptor sites and lead to intracellular regulation of cholesterol metabolism. By contrast, the typical HDL do not interact with cell receptors.[10,13,14]

I must stress that our studies show two distinct types, or subclasses, of HDL—each with different metabolic properties (Figure 5). One subclass of HDL is capable of binding to the cell surface receptors on fibroblasts and smooth muscle cells, the same receptor site that interacts with LDL. This subclass is the HDL with the E apoprotein; however, the second subclass of HDL lacks the E apoprotein (Figure 5) and does not bind to the cell surface receptors of fibroblasts and smooth muscle cells. These two subclasses of HDL occur in both humans and experimental animals and can be quantitatively isolated using heparin-Sepharose affinity chromatography.[15,16]

It is the HDL with the E apoprotein that increase with cholesterol feeding and become the HDL_c. This has been shown in several species of animals in our laboratory and more recently has become evident in studies of humans who have consumed high cholesterol diets. The changes in the HDL following cholesterol feeding are illustrated in Figure 6. In this study we compared the two HDL fractions from a dog fed a low cholesterol (control) diet and then a high cholesterol diet. After cholesterol feeding, the second HDL peak (the HDL with the E apoprotein) was increased. In this particular example, the HDL with E apoprotein (the HDL_c) increased fourfold within four days after cholesterol feeding began. Not only did the mass of HDL with E increase, but the concentration of the E apoprotein in this particular lipoprotein also increased.[16]

In studies of normal humans, we have shown that binding activity of HDL to the cell surface receptors of fibroblasts can be increased three- or fourfold by eating a high cholesterol diet in the form of four to six eggs per day.[17] In Figure 7 the binding activity of the HDL before and after cholesterol feeding are compared in two subjects. The binding activity of the HDL from both subjects increased after the addition of the cholesterol to the diet. This is an indication of the more direct data that we now have showing that the HDL_c (the HDL with the E apoprotein) are increasing in human plasma just as we have shown in the several animal species (E. Flaim, T. P. Bersot and R. W. Mahley, in preparation). We have now studied over a dozen such subjects with similar results.

It is important to note that the changes in the

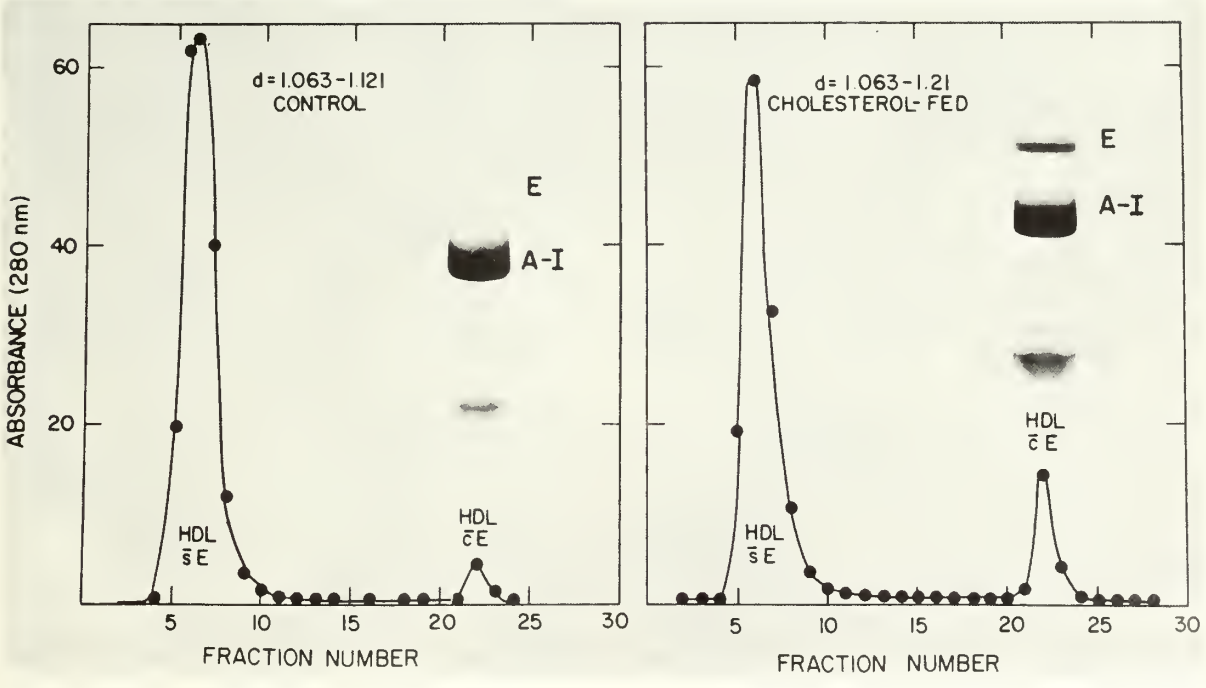


Figure 6.—Elution profile from a heparin-Sepharose affinity column of canine HDL (d = 1.063-1.21) before (control) and after four days of cholesterol feeding. (HDL$\bar{c}$E = high-density lipoproteins with E apoprotein; HDL$\bar{s}$E = high-density lipoproteins without E apoprotein.)

HDL occurred without regard to plasma cholesterol levels (Figure 7). In both subjects the plasma cholesterol was approximately 200 mg per dl before the high cholesterol diet. During the four-week feeding study, the plasma cholesterol in subject 1 did not change at all. In subject 2, the plasma cholesterol rose by 23 percent. However, in both subjects a change in the metabolic activity of the HDL occurred. Therefore, subtle metabolic changes can occur in specific lipoproteins with or without gross changes in the cholesterol content of the plasma, and these changes can affect the ways in which these lipoproteins interact with cells and regulate cholesterol metabolism.

Thus, by studying the various normal and cholesterol-induced lipoproteins, we have found that LDL and certain types of HDL (HDL containing the E apoprotein) can bind to receptors on the surface of the cells and regulate intracellular cholesterol metabolism in fibroblasts and arterial smooth muscle cells. These studies show much about how lipoproteins interact with cells. However, it is hard to explain atherosclerosis on the basis of these results. The receptor-mediated uptake process is self-regulating; a feedback system allows fibroblasts and smooth muscle cells to take up only a limited amount of cholesterol before the availability of cell surface receptors is repressed. Smooth muscle cells and fibroblasts will not accumulate large amounts of cholesterol regardless of which lipoproteins are exposed to the cells. Thus, they simply will not load themselves with fat and become the lipid-laden foam cells seen in the atherosclerotic lesion.

The Macrophage and B-VLDL

Then, what are those lipid-filled cells in the atherosclerotic lesion? What is the source of their cholesterol? Which of the lipoproteins are responsible for the delivery of cholesterol to these cells? If the lipid-laden foam cells in an atherosclerotic lesion are smooth muscle cells, then they are no longer able to regulate lipoprotein uptake, and thus continue to take up cholesterol. However, these foam cells may actually be another cell type, for example, *the macrophage*. That foam cells originate from macrophages is an appealing hypothesis. The cholesterol-fed dog and other animals used in our experiments are providing us with important information about the cell type and the lipoproteins involved. The cells that accumulate the cholesterol strongly resemble macrophages, as do the cells that occur in certain types

CHOLESTEROL INDUCED CHANGES IN HUMAN HDL

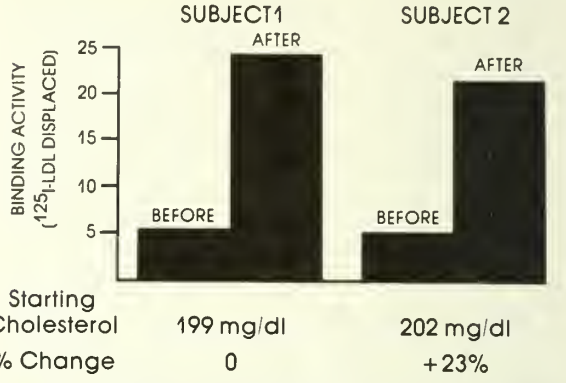


Figure 7.—Ability of human high-density lipoproteins (HDL, d = 1.095-1.21) to compete with low-density lipoproteins (LDL) labeled with iodine 125 for binding to the cell surface receptors of cultured human fibroblasts. Comparisons made between HDL obtained before and after addition of 4 to 6 eggs per day to both subjects' diets for four weeks. (See Mahley et al[17] for description of results.)

of human atherosclerosis. The lipoproteins that deposit cholesterol and accelerate atherosclerosis appear to be the β-very-low-density lipoproteins (B-VLDL).

Dogs do not naturally develop any arterial lesions that can be called atherosclerosis. Atherosclerosis can be induced in dogs only when the plasma cholesterol level is maintained by high fat, high cholesterol diets in excess of 750 mg per dl for more than six months. In these animals (called hyperresponders), severe lipid-laden lesions develop, which are associated with complicated atherosclerosis and, in some cases, occlusive thrombosis.[13,18,19] In dogs with diet-induced hypercholesterolemia of 350 to 700 mg per dl atherosclerosis does not develop at all, even after one or two years on the diet (such animals are called hyporesponders). We turned to detailed studies of the lipoproteins in an attempt to understand how plasma cholesterol levels as high as 350 to 700 mg per dl were nonatherogenic, but levels only slightly higher (in excess of 750 mg per dl) were highly atherogenic.

Figure 8 compares the electrophoretic patterns of a control dog and four cholesterol-fed dogs. The plasma cholesterol levels of the cholesterol-fed dogs (two hyporesponders and two hyperresponders) are indicated on the patterns. The lipoproteins of the control dog include the LDL and two α-migrating lipoproteins referred to as HDL_1 and HDL_2. HDL_1 are the high-density lipoproteins that contain the E apoprotein, and the HDL_2

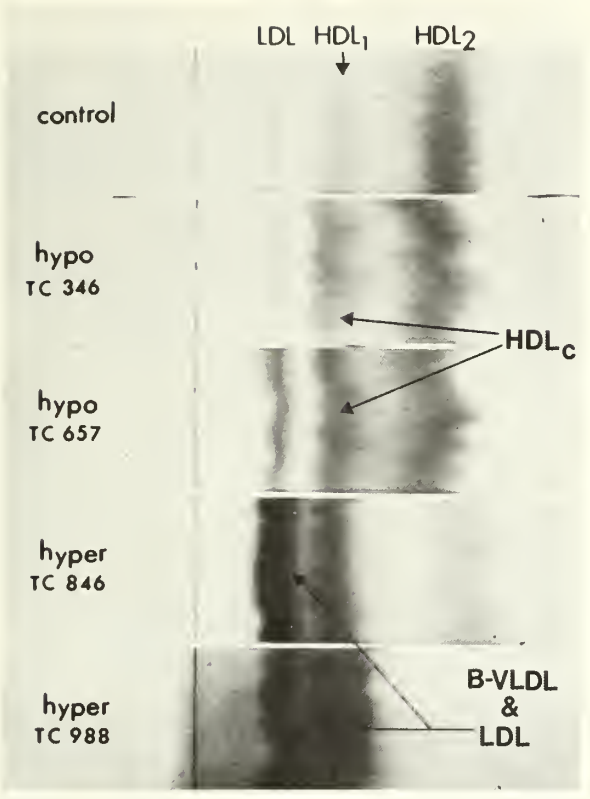


Figure 8.—Paper electrophoretograms of the plasma lipoproteins of a control dog (top strip) and four different cholesterol-fed dogs with variable degrees of hypercholesterolemia (HDL = high-density lipoproteins; LDL = low-density lipoproteins; TC = total plasma cholesterol in mg/dl). (Reproduced with permission from the American Heart Association, Inc.; from Mahley et al.[20])

are the high-density lipoproteins that lack the E apoprotein. As plasma cholesterol levels increase with cholesterol feeding, the principal lipoprotein to carry the cholesterol is the one with α_2-mobility like the HDL_1. In the cholesterol-fed dog, HDL_1 is the HDL_c. Also, as the plasma cholesterol levels increase, the LDL concentration increases. Thus, in the hyporesponders, there are two major changes: an increase in the LDL and the appearance of the HDL_c and, remember, no atherosclerosis.[13]

The dogs in which atherosclerosis developed (the hyperresponders with plasma cholesterol levels in excess of 750 mg per dl) present a more complicated electrophoretic pattern. There is a broad β, pre-β band. This correlates with the presence of the B-VLDL, already discussed. These animals also have an increase in the LDL. As can be noted in Figure 8, the HDL_c remain prominent, and there is a reduction in the typical HDL. At the risk of oversimplification—there are two major differences between the nonatherogenic hyperlipidemia and the atherogenic hyperlipidemia. These are the appearance of B-VLDL and the decrease in the typical HDL.

Our attention has focused in recent months on the B-VLDL as a likely candidate for the atherogenic lipoprotein and on *the macrophages* as the cells likely to accumulate the cholesterol in the arterial wall. We designed studies to determine if any of the normal or cholesterol-induced lipoproteins are taken up by macrophages in culture. We found that, of all the naturally occurring lipoproteins, only the B-VLDL will cause cholesterol to accumulate in macrophages. VLDL, LDL and HDL from normal animals and LDL and HDL_c from cholesterol-fed animals will not cause the massive deposition of cholesterol in macrophages. Cholesterol deposition (primarily cholesteryl esters) occurs only from the B-VLDL. Macrophages incubated with B-VLDL have a 20- to 160-fold increase in cholesteryl ester content. The uptake is mediated by a high-affinity cell surface receptor that is specific for B-VLDL. In cholesterol-fed dogs, the B-VLDL cause the accumulation of cholesterol; these lipoproteins are also responsible for such accumulation in cholesterol-fed monkeys, rats and rabbits. The B-VLDL from all of these species load macrophages with cholesteryl esters.[13]

Preliminary data suggest that cholesterol feeding in humans causes the appearance of lipoproteins resembling B-VLDL. These lipoproteins may be present transiently in the plasma after a high fat, high cholesterol meal. It is reasonable to speculate, on the basis of the animal studies, that these lipoproteins (B-VLDL) may appear repeatedly as we overindulge in high fat, high cholesterol meals, and that over the years this could lead to deposition of cholesterol in the arterial wall. These studies in animals and humans suggest that high levels of dietary lipids alter several different types of plasma lipoproteins, change the way cholesterol is transported in the plasma and alter the metabolic manner in which these various lipoproteins interact with cells. High levels of dietary cholesterol cause some of these changes in plasma lipoproteins with or without altering the plasma cholesterol levels.

Summary

When diets high in fat and cholesterol are fed to different species of animals, they cause significant changes in various classes of lipoproteins, including the appearance of B-VLDL, an increase in LDL, the appearance of HDL_c and the decrease in typical HDL. Similar, but more subtle changes,

are being observed in humans—such as the role of these lipoproteins in the cellular metabolism of cholesterol. Smooth muscle cells and fibroblasts take up B-VLDL, LDL and IDL_c via specific cell surface receptors that recognize the lipoproteins that contain the B and E apoproteins. However, the amount of cholesterol that can accumulate in smooth muscle cells or fibroblasts is closely regulated, preventing the conversion of these cells to the lipid-laden foam cells characteristic of atherosclerosis. It is intriguing that macrophages, however, do accumulate large amounts of cholesteryl esters when presented with the cholesterol-induced B-VLDL from various species, but not in response to any of the other naturally occurring lipoproteins.

I believe that when one looks at all of the pieces of the puzzle, including population and epidemiologic data and diet experiments in animals, it is evident that dietary fat and cholesterol are, indeed, linked to accelerated cardiovascular disease. The American public should not ignore the recommendations of the American Heart Association and of the various governmental agency reports that recommend a prudent diet low in cholesterol and saturated fat. And in this regard, I must disagree with the conclusions of the Food and Nutrition Board.

REFERENCES

1. National Academy of Sciences Food and Nutrition Board: Toward Healthful Diets. Washington, DC, Food and Nutrition Board, National Research Council, 1980

2. Connor WE, Connor SL: The key role of nutritional factors in the prevention of coronary heart disease. Prev Med 1:49-83, 1972

3. Keys A: Coronary heart disease—The global picture. Atherosclerosis 22:149-192, 1975

4. Stamler J: Population studies, *In* Levy RI, Riskind BM, Dennis BH, et al (Eds): Nutrition, Lipids and Coronary Heart Disease. New York, Raven Press, 1979, pp 25-28

5. Keys A: Coronary heart disease, serum cholesterol, and the diet. Acta Med Scand 207:153-160, 1980

6. Mahley RW: Cholesterol-induced hyperlipoproteinemia and atherosclerosis in dogs, swine and monkeys: Models for human atherosclerosis, *In* Gotto AM Jr, Smith LC, Allen B (Eds): Atherosclerosis—V. New York, Springer-Verlag, 1980, pp 355-358

7. Armstrong ML, Megan MB, Warner ED: Intimal thickening in normocholesterolemic rhesus monkeys fed low supplements of dietary cholesterol. Circ Res 34:447-454, 1974

8. Mahley RW: Alterations in plasma lipoproteins induced by cholesterol feeding in animals including man, *In* Dietschy JM, Gotto AM Jr, Ontko JA (Eds): Disturbances in Lipid and Lipoprotein Metabolism. Bethesda, MD, American Physiological Society, 1978, pp 181-197

9. Mahley RW, Weisgraber KH, Innerarity T, et al: Characterization of the plasma lipoproteins and apoproteins of the erythrocebus patas monkey. Biochemistry 15:1928-1933, 1976

10. Mahley RW, Innerarity TL, Weisgraber KH: Alterations in metabolic activity of plasma lipoproteins. Ann NY Acad Sci 348: 265-277, 1980

11. Sherrill BC, Innerarity TL, Mahley RW: Rapid hepatic clearance of the canine lipoprotein containing only the E apoprotein by a high affinity receptor. J Biol Chem 255:1804-1807, 1980

12. Goldstein JL, Brown MS: The low-density lipoprotein pathway and its relation to atherosclerosis. Ann Rev Biochem 46:897-930, 1977

13. Mahley RW: Cholesterol feeding: Effects on lipoprotein structure and metabolism, *In* Gotto AM Jr, Smith LC, Allen B (Eds): Atherosclerosis—V. New York, Springer-Verlag, 1980, pp 355-358

14. Innerarity TL, Mahley RW: Enhanced binding by cultured human fibroblasts of apo-E containing lipoproteins as compared to low-density lipoproteins. Biochemistry 17:1440-1447, 1978

15. Weisgraber KH, Mahley RW: Subfractionation of human high density lipoproteins by heparin-Sepharose affinity chromatography. J Lipid Res 21:316-325, 1980

16. Mahley RW, Weisgraber KH: Subfractionation of high-density lipoprotein into two metabolically distinct subclasses by heparin-Sepharose affinity chromatography and Geon-Pevikon electrophoresis, *In* Lippel K (Ed): Report of the High Density Lipoprotein Methodology Workshop, NIH Publication, No. 79-1661. Washington, DC, US Dept of Health, Education, and Welfare, 1979, pp 356-366

17. Mahley RW, Innerarity TL, Bersot TP, et al: Alterations in human high-density lipoproteins, with or without increased plasma-cholesterol, induced by diets high in cholesterol. Lancet 2:807-809, 1978

18. Mahley RW, Nelson AW, Ferrans VJ, et al: Thrombosis in association with atherosclerosis induced by dietary perturbations in dogs. Science 192:1139-1141, 1976

19. Mahley RW, Innerarity TL, Weisgraber KH, et al: Canine hyperlipoproteinemia and atherosclerosis—Accumulation of lipid by aortic medial cells in vivo and in vitro. Am J Path 87:205-225, 1977

20. Mahley RW, Weisgraber KH, Innerarity T: Canine lipoproteins and atherosclerosis—II. Characterization of the plasma lipoproteins associated with atherogenic and nonatherogenic hyperlipidemia. Circ Res 35:722-733, 1974

Important Advances in Clinical Medicine

Epitomes of Progress — Dermatology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in dermatology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in dermatology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Dermatology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

High Doses of Aspirin in the Treatment of Mucocutaneous Lymph Node Syndrome

THE INFANTILE ACUTE febrile mucocutaneous lymph node syndrome (MLNS) was first reported in Japan by Kawasaki and his associates, but has since been reported world-wide. As of this writing the cause is still unknown.

Kawasaki disease occurs primarily in young children and is characterized by a prolonged febrile course, polymorphous rash, telangiectasia of the bulbar conjunctivae, lymphadenopathy, striking redness of the palms and soles, nonpitting edema of the backs of the hands and feet, and unique desquamation of the skin under the finger nails during recovery. During the acute phase (first month), myocarditis, pericarditis and congestive heart failure may occur. During the second month (recovery phase), myocardial infarction is possible. The mortality is about 1 percent to 2 percent. No specific treatment has been available and aspirin (acetylsalicylic acid) in usual doses has not controlled the fever.

During a recent epidemic of MLNS in New York, Jacobs, a rheumatologist, was able to show that it was impossible to attain therapeutic salicylate levels (20 mg per dl) in the acute phase of the illness with less than a total daily dose of 140 mg per kg of body weight. In fact, many children required daily doses of between 150 and 200 mg per kg of body weight. As the children recovered, serum levels of aspirin rose and dosage had to be lowered to conventional amounts (100 mg per kg of body weight per day).

Typically, patients became afebrile when the serum salicylate level reached approximately 20 mg per dl. Patients were found to malabsorb aspirin (and perhaps also to destroy it) and so required extraordinarily high doses during the acute phase of the illness.

In addition to aspirin therapy, Jacobs treated those patients with life-threatening conditions (usually congestive heart failure) with prednisone. He found that extraordinarily high doses of prednisone (for example, 3 mg per kg of body weight per day) were also required in Kawasaki disease.

Jacobs concluded that early recognition and prompt institution of effective therapy has resulted in greatly reducing the average stay in hospital. Levels of salicylate in the blood must be determined each day for dose adjustment. Because of

the high incidence of aneurysms of the coronary arteries, extreme thrombocytosis and myocardial infarction during the recovery period, aspirin therapy in conventional doses was continued for two months after onset of the disease. All patients in this series recovered completely.

Kato and associates in Japan have also studied the effect of treatment of MLNS by means of coronary angiography during the recovery phase of the illness. Although they were apparently unaware of the need for high-dose therapy during the acute phase, they were able to show a definite reduction in frequency of coronary aneurysms in patients on prolonged aspirin therapy.

ALVIN H. JACOBS, MD

REFERENCES

Kawasaki T, Kosaki F, Okawa S, et al: A new infantile febrile mucocutaneous lymph node syndrome (MLNS) prevailing in Japan. Pediatrics 54:271-276, Sep 1974

Jacobs JC: Case report—Salicylate treatment of epidemic Kawasaki disease in New York City. Therapeutic Drug Monitoring 1: 123-130, 1979

Kato H, Hoike S, Yokoyama T: Kawasaki disease: Effect of treatment on coronary artery involvement. Pediatrics 63:175-179, Feb 1979

Acral Lentiginous Melanoma

ACRAL LENTIGINOUS MELANOMA (ALM) is a relatively recent addition to the clinicohistopathologic classification of melanomas. Clark and co-workers in 1975 and Reed in 1976 developed the concept of this variant to describe lesions characterized by lentiginous macules occurring on the palms, soles and subungual areas. Traditionally, the three variants of cutaneous melanoma are categorized as lentigo maligna melanoma (LMM), superficial spreading melanoma (SSM) and nodular melanoma (NM). ALM represents a fourth group and is reported to constitute 7 percent to 9 percent of all melanomas.

Clinically, ALM resembles LMM in that the lesions are frequently macular, may be irregular in shape and may show variation in pigmentation. In contrast to LMM, these lesions usually do not occur in sun-exposed areas of the skin and are distributed in regions that are free of hair.

Both sexes are at equal risk for the development of ALM. The age at onset is usually in the third through sixth decades, which is similar to the onset of SSM and NM. Although relatively uncommon in whites, ALM may account for up to 50 percent of melanomas occurring in blacks.

Histologically, ALM may appear to be innocuous in the radial growth phase, demonstrating only a diffuse hyperplasia of melanocytes in the basal epidermal layer. The melanocytes may range in character from benign-appearing spindled or epithelioid cells to bizarre and dysplastic cells. There is usually an absence of epidermal atrophy and dermal actinic damage in ALM, both prominent features of LMM. In the vertical growth phase, desmoplasia (not an uncommon feature of LMM) is also observed in ALM.

It is essential to obtain a biopsy specimen of a suspected ALM, and an in toto excision is preferable as there may be a gradation of melanocytic dysplasia from the periphery to the central portion, with some areas showing only minimal cellular atypia.

Treatment of digital ALM is by "ray amputation," which includes the entire digit plus the distal portion of the corresponding metatarsal or metacarpal bone. Lesions of the thumb may be treated by disarticulation of the metacarpophalangeal joint, which allows for subsequent reconstruction and, therefore, maintenance of apposition. Volar lesions are best removed by wide excision.

The mechanism of spread of ALM is not yet adequately described. At present, there are insufficient statistical data available on aspects such as the level and depth of invasion, mitotic activity and host response to propose definite indications for lymph node dissection, and similarly, more sophisticated forms of management of these lesions.

DAVID R. TAYLOR, Jr, MD

REFERENCES

Kopf AW, Bart RS, Rodriguez-sains RS: Malignant melanoma: A review. J Dermatol Surg Oncol 3:41-125, Jan-Feb 1977

Taylor DR Jr, South DA: Acral lentiginous melanoma. Cutis 26:35-36, Jul 1980

Coleman WP III, Loria PR, Reed RJ, et al: Acral lentiginous melanoma. Arch Dermatol 116:773-776, Jul 1980

Newer Aspects of the Use of Anthralin in Psoriasis

ANTHRALIN IS AN effective agent in the treatment of psoriatic lesions in patients in hospitals or day care centers. It is administered in concentrations of 0.1 percent to 1.0 percent in a hard or soft paste and may be used in combination with topically administered tars or steroids, and ultraviolet light. Clearing can be expected in 10 to 28 days. A pomade containing anthralin 0.1 percent to 1.0 percent can produce excellent results in psoriasis of the scalp. The method of action of anthralin is not yet clear; however, it is known to bind to DNA in vitro, and presumably inhibits DNA synthesis.

The major problems that prevent more successful and widespread use of standard anthralin regi-

mens for outpatients are the following: (1) Burning of normal skin by higher concentrations necessitates careful application of the stiff paste on the lesions by a skilled nursing staff; (2) anthralin can stain bedclothes and sheets, making home use difficult; (3) prolonged applications are sometimes needed; (4) anthralin should not be used in skin folds, and (5) if anthralin inadvertently gets in the eyes, severe burning may result. These problems have been partially overcome by the newer methods of application discussed below.

Schaefer and co-workers used 1 percent anthralin with 1 percent salicylic acid in petrolatum, which they applied to the psoriatic lesions each day; the ointment was left on for one hour and then removed with soap and water. As far as possible, the anthralin should not be placed on normal appearing skin because this may cause erythema and a burning sensation. It is preferable to follow each treatment with application of an emollient ointment or cream. If this regimen is continued daily, it is successful in clearing 30 percent of the psoriatic lesions and improving an additional 50 percent. The advantage of this method is its short application time, which allows a patient to use anthralin while relaxing at home and avoids staining clothes and sheets. The chief disadvantage is occasional burning that may occur around treated plaques.

In Sweden, Brody and Johansson used 0.01 percent to 0.03 percent anthralin with 10 percent salicylic acid in petrolatum on a daily basis. This ointment does not need to be so carefully applied to lesions only, as burning of normal skin is rarely seen. It usually does not stain clothing so the ointment may be applied in the evening and morning. The main disadvantage is the slow response of lesions, which may take up to three months to resolve.

In England, Seville and co-workers compared the use of 0.25 percent anthralin in a cream base (Dithrocream; dithranol is the generic name) with 0.25 percent anthralin in an ointment base. He found the two preparations to be equally effective. However, patients preferred the easier application of the cream base although it caused more staining than the ointment base.

Anthralin continues to be an important agent in the inhospital treatment of patients with psoriasis. Newer methods of application are making its use possible to outpatients as well.

LEONARD H. GOLDBERG, MD
MARGARET STEWART, MD

REFERENCES

Harris DR, Ferrington RA: The chemistry, pharmacology, and use of anthralin in the treatment of psoriasis, chap 39, *In* Farber EM, Cox AJ (Eds): Psoriasis—Proceedings of the International Symposium. Stanford, CA, Stanford University Press, 1971, pp 357-365

Schaefer H, Farber EM, Goldberg L, et al: Limited application period for dithranol in psoriasis. Brit J Dermatol 102:571-573, May 1980

Brody I, Johansson A: A topical treatment program for psoriasis with low anthralin concentrations. J Cutan Pathol 4:233-243, Oct 1977

Seville RH, Walker GB, Whitefield M: Dithranol cream. Brit J Dermatol 100:475-476, Apr 1979

Lymphomatoid Papulosis

THE CLINICAL AND HISTOLOGICAL assessment of patients with atypical infiltrates suggestive of lymphoma or leukemia but confined only to the skin has been a difficult problem for many years. In some of these patients involvement of other organs occurs within a short time and a definite diagnosis can be made. In others, however, crops of lesions may continue to develop for many years. These lesions spontaneously resolve within a few weeks and are accompanied by no other evidence of neoplastic disease. The term lymphomatoid papulosis, proposed by Macaulay in 1978, has been the most popular designation for this latter group.

The most common clinical pattern is an inflammatory papular or papulonecrotic eruption that is indistinguishable from pityriasis lichenoides acuta (Mucha-Habermann disease). Mycosis fungoides may be difficult to exclude but clinical evidence of small, short-lived papulonecrotic lesions as well as histological evidence of hemorrhage and epidermal necrosis are said to favor a diagnosis of lymphomatoid papulosis. The relationship of lymphomatoid papulosis to pityriasis lichenoides and, indeed, the nature of pityriasis lichenoides, both remain unclear. It is interesting that in some patients with this clinical pattern the condition responds favorably to ultraviolet light exposure.

Clinical diagnosis is made even more difficult by the fact that some of these patients have papular, plaque-type or nodular lesions that do not resemble pityriasis lichenoides. These lesions generally show less clinical and histological evidence of inflammation and are more suggestive of the tumors of mycosis fungoides or other lymphomas, but still may wax and wane for many years.

Although the great majority of patients reported in the literature have experienced a prolonged benign course, there have been at least three cases in which visceral lymphoma developed and one that has evolved into the more usual pattern of

mycosis fungoides. The significance of the different clinical patterns is not clear at present, but it seems likely that "lymphomatoid papulosis" is not a single disease entity. The application of recently developed immunological methods may help to better define the nature of these perplexing eruptions and their relationship to lymphoid neoplasia.

At present there is no specific therapy for these eruptions and it is clear that these patients should be kept under periodic observation.

DAVID G. DENEAU, MD

REFERENCES

Macaulay WL: Lymphomatoid papulosis. Int J Dermatol 17: 204-212, Apr 1978

Black MM, Jones EW: "Lymphomatoid" pityriasis lichenoides: A variant with histological features simulating a lymphoma—A clinical and histopathological study of 15 cases with details of long term follow up. Br J Dermatol 86:329-347, Apr 1972

Valentino LA, Helwig EB: Lymphomatoid papulosis. Arch Pathol 96:409-416, Dec 1973

Lutzner M, Edelson R, Schein P, et al: Cutaneous T-cell lymphomas: The Sezary syndrome, mycosis fungoides, and related disorders. Ann Int Med 83:534-552, Oct 1975

Inflammatory Lesions of Acne Vulgaris: Current Concepts

PATHOGENIC MICROORGANISMS are not commonly present in the inflammatory lesions of acne, and the microorganisms that are present do not invade and multiply in the tissues. Thus, these inflammatory lesions do not involve an infection in the usual sense.

Minor inflammatory lesions are small, very superficial, immediately perifollicular and intrafollicular, short-lived and usually heal without scarring. Such lesions may be benefited by topical therapy. They appear to be the consequence of polymorphonuclear leukocyte aggregation in response to chemotactic factors in the follicle.

Major inflammatory lesions begin deeper (in the dermis), forming nodules of varying size and severity, often persisting for a long time. The crucial event responsible is disruption of the follicle wall with escape of follicle contents into the dermis. The contents include disintegrated epithelial and sebaceous cells, sebum in varying stages of chemical change, microflora including anaerobic *Propionibacterium acnes,* aerobic *Staphylococcus epidermidis,* yeasts, metabolites of these organisms (lipase, proteases and others), free fatty acids, squalene, keratin and hair fragments. Many of these are antigenic and when combined with lipids with adjuvant properties, have the potential for induction of immune reactions. Others can cause primary irritation and foreign body reactions. Thus, the follicle contents include a variety of possible pathogenic agents.

Histologically, the major lesions present elements of mixed granuloma, and infiltrates of polymorphonuclear leukocytes, histiocytes, macrophages and lymphocytes. Fibroblasts and newly formed capillaries are commonly observed. Vasculitis is not present. Hemorrhage and necrosis with ulceration may occur and scarring can be severe.

To prevent the occurrence of major lesions it is necessary to block those mechanisms which disrupt the follicle wall. A frequent finding in early lesions is the invasion of the follicle wall by polymorphonuclear leukocytes with abscess formation. Release of lytic and toxic agents, which may damage the wall, would be a likely consequence. The concept that obstruction of the follicle ostium with subsequent build up of sebum, formation of a comedo, and pressure rupture of the follicle is untenable because it has been shown that disruption occurs in follicles in which obstruction and gross comedones are not present.

In view of the nature of the lesions and the absence of active infection, it is not unexpected that antibacterial agents exert no major beneficial effect on existing inflammatory lesions, and there are no controlled data to show that they do. To the extent that they are effective, it is by decreasing the occurrence of new lesions. Presumably, the mechanism is by reduction of the bacterial population of susceptible follicles.

Existing inflammatory lesions do respond to nonspecific antiinflammatory agents, particularly corticosteroids, either by local or systemic routes of administration. When severe lesions in great numbers are present, systemic therapy is required. In certain cases, for reasons unknown, intensely inflammatory lesions supervene in what had been mild and not otherwise unusual acne vulgaris. The lesions are characterized by pain, hemorrhage, sterile suppuration, gelatinous granulation tissue, liquifying necrosis, ulceration and severe scarring. In some instances the onset has been preceded by viral infections, measles and infectious mononucleosis, or periods of extreme emotional stress. In many cases, no trigger factors are recognized. The nature and pathogenesis of the lesions have not been clarified.

This subject was comprehensively reviewed by Goldschmidt and co-workers in a report in 1977. Systemic corticosteroid therapy was necessary for control. Most cases reverted to their previous state

of relatively mild inflammatory acne after corticoid therapy, suggesting the possibility of altered reactivity.

JUD R. SCHOLTZ, MD

REFERENCES

Goldschmidt H, Leyden JJ, Stein KH: Acne fulminans: Investigation of acute febrile ulcerative acne. Arch Dermatol 113:444-449, Apr 1977

Esterly NB, Furey NL: Acne: Current concepts. Pediatrics 62: 1044-1055, Dec 1978

Whiting DA: Acne (Clinical Review). West J Med 131:551-557, Dec 1979

Update on the Use of Retinoids

THE TERM RETINOID refers to vitamin A in all its naturally occurring forms, as well as to the various synthetic analogues that have been developed. Various retinoids, particularly transretinoic acid, vitamin A alcohol (retinol) and certain retinol esters, have been used by dermatologists for many years in the treatment of several cutaneous disorders, especially those characterized by abnormal keratinization. However, the clinical usefulness of these older derivatives has been limited by their side effects. Common side effects resulting from therapeutically useful dosages of transretinoic acid include headache, anorexia, flushing, fatigue and dryness of the lips and skin. Less common side effects include nausea, polydipsia, dizziness, petechiae, loss of hair, increased perspiration, dryness of nasal mucosa, dandruff, psychological disturbances, facial edema and changes in pruritus. In addition, chronic vitamin A excess has been noted to cause joint and bone pain, prominence and irritation of the eyes, hepatomegaly, splenomegaly, urinary frequency and urgency, and increased intracranial pressure with concurrent neurological signs (more common in children and adolescents). In contrast to the poor therapeutic index of the older retinoids, some of the newer derivatives, especially 13-cis-retinoic acid and an aromatic retinoic acid derivative RO 10-9359, appear to be more effective with less toxicity.

Complete to nearly complete clearing (greater than 90 percent) in patients with lamellar ichthyosis, pityriasis rubra pilaris and keratosis follicularis has been reported in recent trials with the use of these new retinoids. However, data concerning relapse after discontinuing therapy, as well as ideal initial dosage and dosages for maintenance therapy, have not yet been determined.

Several investigators have also reported the clinical usefulness of RO 10-9359 in the treatment of psoriasis. In many trials, about 50 percent of the patients treated have had good to complete clearing. It is noteworthy that most patients chosen for these trials have severe chronic psoriasis and are often recalcitrant to conventional therapy. This new aromatic retinoid also appears to be effective in erythrodermic and pustular psoriasis. It has been shown to be an effective oral adjuvant in psoriasis therapy, increasing the clinical efficacy of more conventional treatment regimens such as topical anthralin, ultraviolet B (UVB) radiation, and psoralen combined with ultraviolet A (UVA) radiation.

The derivative 13-cis-retinoic acid has been used effectively in the treatment of cystic and conglobate acne. Peck and co-workers reported complete clearing in 13 of 14 patients with resistant cystic and conglobate acne who used 13-cis-retinoic acid. It is significant that prolonged remissions were observed in all the patients treated, lasting as long as 20 months after discontinuation of therapy.

Finally, preliminary investigations indicate that the new retinoids may be effective in the treatment of basal cell carcinomas. Peck and co-workers treated 11 patients with multiple basal cell carcinomas induced by sunlight, irradiation, arsenic or the basal cell nevus syndrome. Orally given 13-cis-retinoic acid was used and of the 248 tumors treated, 39 (16 percent) underwent complete clinical regression. Biopsy specimens were obtained after treatment for 35 of the 39 tumors; 21 of them showed complete histological clearance. Of the remaining tumors, 162 (65 percent) decreased in size and 47 (19 percent) were unchanged after treatment.

With regard to toxicity, it appears that the adverse effects observed with these two new retinoids are usually mild and rarely, if ever, severe enough to discontinue therapy. The most common side effects noted have been limited primarily to the skin and mucous membranes, which can result in various minor disturbances such as cheilitis, facial dermatitis, xerosis, dry nasal mucosa, minor nosebleeds, conjunctivitis, increased skin fragility, inflamed urethral meatus, paronychia, hair thinning, dry hair and a palmo-plantar desquamation. Other less common side effects include changes in appetite, increased thirst, headache and arthralgias without evidence of arthritis. Temporary slight elevations of the serum transaminases have also been observed in patients receiving the new retinoids. According to Peck and co-workers, this occurs in 10 percent to 15 percent of patients, but the importance of these changes is unclear because

they appear to be transient, returning to normal in two to four weeks even with continued therapy. Also, elevations of triglycerides and very low-density lipoproteins have been noted with the use of the new retinoids, but the exact incidence, long-term importance and effect of dietary management on these elevations have not been determined. Again these recognized toxicities, besides being generally mild, are usually treatable with innocuous therapies, are dose dependent in severity and incidence, and are reversible after discontinuing therapy.

The mechanism of action of the retinoids is unknown. Vitamin A is known to be necessary for maintenance of normal cellular differentiation of epithelial tissues. This property probably accounts, at least in part, for the therapeutic efficacy of retinoids. In addition, investigations indicate that the usefulness of 13-cis-retinoic acid in the treatment of acne may involve a direct inhibitory effect of the drug on sebaceous glands.

The new retinoids may become an extremely useful therapeutic modality for the treatment of certain dermatoses. However, further investigations need to be undertaken to determine their exact mechanism of action, efficacy in controlled trials, chronic toxicity, and the ideal dosages for initial and maintenance treatment.

DANIEL A. PARDINI, MD

REFERENCES

Peck GL, Yoder FW: Treatment of lamellar ichthyosis and other keratinising dermatoses with an oral synthetic retinoid. Lancet 2:1172-1174, Nov 1976

Peck GL, Olsen TG, Yoder FW, et al: Prolonged remissions of cystic and conglobate acne with 13-cis-retinoic acid. N Engl J Med 300:329-333, Feb 15, 1979

Peck GL: Retinoids in dermatology—An interim report. (Editorial). Arch Dermatol 116:283-284, Mar 1980

New Developments in the Staging and Therapy of Mycosis Fungoides

THE STAGING OF patients with mycosis fungoides is now based on two criteria: the ability to confirm the diagnosis of the disease in skin infiltrates and the ability to evaluate the extent of involvement in the patient's lymphoreticular system. The diagnosis of mycosis fungoides in the skin is made according to the extent of infiltration into the epidermis. The presence of numerous, large aggregates of abnormal lymphocytic cells or a diffuse and dense infiltrate of these cells within the epidermis indicates the presence of the disease. If there are only small aggregates or a patchy diffuse infiltration of these abnormal lymphocytic cells, then an accurate diagnosis cannot be confirmed unless there is also a dense infiltrate in the reticular dermis. Further biopsy specimens may be needed to confirm the diagnosis. Evaluation of lymph nodes is made by obtaining biopsy specimens of the superficial regional glands. A bipedal lymphangiogram should be obtained to evaluate the internal nodes. A biopsy is mandatory if the lymphangiogram shows abnormal nodes or if there is extensive skin infiltration.

Recent studies in patients in various stages of the disease showed a progressive decrease in the immunologic response, as manifested by lymphoblast transformation to phytohemagglutinin and to cells cultured from mycosis fungoides plaques on the skin as one passes through increasingly involved stages of the disease. Similarly, there is a progressive decrease in the stimulation index when the patient's peripheral blood lymphocytes are utilized as responder cells in mixed lymphocyte cultures. Different types of sera added to the culture media have either an inhibitory or facilitory effect and are found to be nonspecific and without correlation to the extent of disease.

New observations in the therapy of mycosis fungoides include the finding that mechlorethamine, when compounded in a hydrophobic vehicle (Aquaphor), instead of an aqueous solution, is more readily tolerated by the patients. In fact, it is associated with a much lower incidence of contact dermatitis as compared with the aqueous solution. Preliminary studies showed that in eight patients with no previous history of exposure or hypersensitivity to mechlorethamine, all tolerated the therapy without complication. In eight other patients with a history of pronounced hypersensitivity to mechlorethamine and an inability to become desensitized, six tolerated the mechlorethamine in Aquaphor. The other two had an immediate hypersensitivity reaction coupled with the unexpected result of immediate clearing of their mycosis fungoides. To date, the average duration of treatment using the Aquaphor vehicle has been 9 months with a range of 1 to 14 months.

Psoralens and ultraviolet light (PUVA; psoralen-ultraviolet A) have been advocated for treatment of mycosis fungoides. However, this form of therapy is effective only as long as the treatment is maintained; when discontinued, the condition usually recurs. PUVA therapy has not been advocated in erythrodermic patients who are usually extremely sensitive to all forms of therapy including electron beam and mechlorethamine. However,

among seven erythrodermic patients who have been treated in the past 24 months with PUVA therapy, clearing of the condition has occurred in six. As observed with other types of mycosis fungoides, there was a recurrence of the disease in the four patients in whom treatment was not maintained. However, subsequent therapy controlled the disease and all the patients are being maintained on PUVA therapy indefinitely.

NORMAN M. PRICE, MB, ChB

REFERENCES

Rappaport H, Thomas LB: Mycosis fungoides: The pathology of extracutaneous involvement. Cancer 34:1198-1229, Oct 1974

Bunn PA Jr, Huberman MS, Whang-Peng J, et al: Prospective staging evaluation of patients with cutaneous T-cell lymphomas—Demonstration of a high frequency of extracutaneous dissemination. Ann Intern Med 93:223-230, Aug 1980

Edelson RL: Cutaneous T-cell lymphoma: Mycosis fungoides, Sezary syndrome, and other variants. J Am Acad Dermatol 2:89-106, Feb 1980

Skin Lesions in Bowel Bypass Syndrome

INTESTINAL BYPASS OPERATIONS as a treatment for morbid obesity have been used since the mid-1950's. Complications have included diarrhea, distention, abdominal pain, pneumatosis cystoides intestinalis, arthralgias, arthritis, renal calculi, gallstones, hepatic abnormalities, electrolyte disturbance and erythema nodosum-like skin eruptions. Three recent articles have reported papulopustular eruptions in six patients following bowel bypass operations.

Hansen and co-workers reported on two patients in whom arthritis, erythema nodosum, and a primarily acral erythematous eruption of papules and pustules developed following jejunoileal bypass operations. The arthritis was minimally responsive to nonsteroid antiinflammatory drugs. Both the arthritis and the skin eruptions improved on treatment with various antibiotic drugs including tetracycline, metronidazole, minocycline and erythromycin. One patient's condition relapsed when antibiotic treatment was withdrawn, but it was later controlled on therapeutic doses of zinc sulfate. Bowel symptomatology was absent. No serological evidence of circulating immune complexes was found. A biopsy specimen of skin from one patient showed an intraepidermal vesicle with a mild leukocytoclastic inflammation of dermal vessels. Direct immunofluorescence of skin was negative.

Goldman and co-workers reported on two patients with end-to-end jejunoileal bypass operations in whom arthralgia, arthritis and a primarily acral erythematous papular and pustular eruption developed. Bowel symptomatology was present in one patient and fever and chills in the other. The first patient responded initially to treatment with penicillin and tetracycline. Subsequently, she did not respond to antibiotic drugs, but did respond to aspirin; later her condition cleared spontaneously. The second patient's condition improved on carbenicillin therapy, while aspirin and nonsteroid antiinflammatory drugs were not helpful. Both patients had elevated erythrocyte sedimentation rates and negative complement 3 and 4 (C3 and C4). The first patient had negative findings on antinuclear antibodies (ANA), rheumatoid factor, cryoglobulin and platelet aggregation tests, but had HLA-B27 positive tissue typing and a positive complement consumption test. The second patient had a negative complement consumption test but a positive platelet aggregation test and ANA-positive 1:320 nucleolar pattern. Biopsy specimens of skin showed a leukocytoclastic vasculitis in both patients. Direct immunofluorescence of skin from the first patient was negative.

Dicken and colleagues reported on two patients who had a primarily acral and upper chest distribution of erythematous papules and pustules, and elevated temperatures following bowel bypass operations. The episodes lasted six days or less and tended to recur. Occasionally, myalgias and polyarthralgia were noted during episodes but not during quiescent periods. The first patient responded to administration of metronidazole. The second patient did not respond to ampicillin therapy but had some decrease in the frequency of eruptions with administration of tetracycline; clearing occurred after surgical restitution of the bypassed segment of bowel. A biopsy specimen of skin from the first patient showed a subepidermal vesicle with heavy mixed-cell dermal inflammation composed of lymphocytes, polymorphonuclear leukocytes and rare plasma cells. No evidence of vasculitis was reported. Direct immunofluorescence showed a patchy, weak basement membrane pattern with C3 but was negative for IgG, IgM and IgA.

The six patients exhibited a primarily acral and upper chest distribution of erythematous papules and pustules. The severity of polyarthralgia or arthritis seemed to parallel the course of the eruption and its response to antibiotic therapy. Serological evidence of circulating immune complexes was found in two of the six cases. Histological

evidence of vasculitis was present in three of four biopsy specimens.

Bacterial overgrowth in the bypassed bowel segments and immune complex formation in response to the excess of bacterial antigens have been suggested as the possible causes of extraintestinal manifestations of the bowel bypass syndrome. The response to antibiotic drugs, evidence of vasculitis in three cases and detection of immune complexes in two cases suggest that a similar pathogenesis may account for papulopustular eruptions seen in bowel bypass patients. However, present therapy is empirical and no single regimen has been consistently beneficial.

FOY W. COX, MD

REFERENCES

Drenick EJ, Ament ME, Finegold SM, et al: Bypass enteropathy—Intestinal and systemic manifestations following small-bowel bypass. JAMA 236:269-272, Jul 19, 1976

Hansen DD, Lopez DA, Jenson KK: Pustulosis associated with bypass surgery for obesity—A dermatoarthritis syndrome. J Assoc Milit Dermatol 4:32-37, Fall 1978

Goldman JA, Casey HL, Davidson ED, et al: Vasculitis associated with intestinal bypass surgery. Arch Dermatol 115:725-727, Jun 1979

Dicken CH, Seehafer JR: Bowel bypass syndrome. Arch Dermatol 115:837-839, Jul 1979

PUVA Carcinogenesis

THE EFFICACY OF PUVA treatment with orally given 8-methoxypsoralen (P) combined with long-wave ultraviolet radiation (UVA) for the clearing of severe psoriasis has been established. The palliative nature of this therapy is evidenced by the recurrence of psoriasis despite continued maintenance therapy once a week or less frequently. Treatment of recurrent psoriasis with PUVA on a more frequent schedule is a common procedure, which over the years may result in a large cumulative UVA irradiation dose expressed in terms of joules per $cm.^2$ The safe upper limit of ultraviolet A dosage from PUVA therapy is not known at this time.

The risk of carcinogenesis from chronic exposure to PUVA has been an early concern. In laboratory animals given large doses of psoralen topically or intraperitoneally plus UV light, a high incidence of squamous cell carcinomas and fibrosarcomas has occurred. The oral administration of psoralen in animals, once thought to be photoprotective, may also produce these tumors in conjunction with UV light. More and more evidence has emerged from in vitro studies that PUVA can be carcinogenic depending on the dose. PUVA has a mutagenic effect in bacterial systems. Sister chromatid exchanges, which have been employed as a cytologic means for the detection of potential carcinogens, have been observed in PUVA cells in vitro but not in vivo. It is known that exposure to nonionizing radiation and to PUVA can affect components of the immune system, which may play a role in photocarcinogenesis.

In humans, a type of epidermal dystrophic change similar to that which occurs in actinic keratoses has been observed in about half of 37 patients treated with PUVA. These changes, which were present at clearing and after a year of therapy, may indicate that cells have been altered genetically by somatic mutation. Whether the epidermal dystrophy is transient or represents a persistent abnormality is being investigated further.

Clinical evidence of PUVA carcinogenicity has emerged from a multicenter follow-up study of more than 1,300 patients. Stern and co-workers documented a total of 48 cases of basal cell and squamous cell carcinomas in 30 patients treated with PUVA during an average observation period of 2.1 years. A significant increase in the incidence of cutaneous cancer was found in patients with previous skin cancers and in those with a history of exposure to ionizing radiation, when compared with the expected risk for an age-sex and geographically-matched population. Of particular concern was an inverse in the expected ratio of basal cell epithcliomas to squamous cell carcinomas, as well as the frequent occurrence of squamous cell carcinomas in areas of the body that were not exposed to the sun. Whether all PUVA-treated patients will be at increased risk for cutaneous carcinogenesis after a longer period of latency has elapsed remains to be determined.

Because of a probable long latent period for carcinogenic effect, younger persons are at greater risk for long-term side effects. For this reason, the Committee on Drugs of the American Academy of Pediatrics has recommended that children not be enrolled in PUVA treatment programs.

A further concern relating to ocular damage following PUVA exposure is based on animal experiments. The exact length of time that photoactive psoralen remains in the lens of the eye is not known. Because of a risk of cataract formation, eyes must be carefully protected with UVA-blocking sunglasses from time of ingestion of psoralen throughout the active treatment program according to published guidelines. During treatment in the light unit, UVA-opaque goggles are worn.

PUVA therapy of psoriasis remains investigational. In selected patients with severe disabling

psoriasis that has been resistant to conventional therapy, PUVA treatment may be administered according to established guidelines with proper precautions taken to minimize potential toxicity to the skin and eyes.

ELIZABETH A. ABEL, MD

REFERENCES

Farber EM, Abel EA, Schaefer H: PUVA appraisal. Br J Dermatol 99:715-717, Dec 1978

Stern RS, Thibodeau LA, Kleinerman RA, et al: Risk of cutaneous carcinoma in patients treated with oral methoxsalen photochemotherapy for psoriasis. N Engl J Med 300:809-813, Apr 12, 1979

Ad hoc Subcommittee on Current Status of Oral PUVA Therapy Epstein JH, Farber EM (Cochairmen), Nall ML (Editor), and 27 compilers and members: Current status of oral PUVA therapy. J Am Acad Dermatol 1:106-117, Aug 1979

Cox AJ, Abel EA: Epidural dystrophy: Occurrence after psoriasis therapy with psoralen and long-wave ultraviolet light. Arch Derm 115:567-570, May 1979

ANA-Negative Systemic Lupus Erythematosus

THE PRESENCE OF antinuclear antibodies (ANA) is generally held to be an important criterion in the diagnosis of systemic lupus erythematosus (SLE). However, careful reading of the literature shows a well-described but generally neglected small group of patients with clinical SLE and negative ANA reactions.

In 1978 Fessel reported on ten patients (whose cases had been followed for ten years) with clinical signs of disease but persistently negative reactions to ANA. Each of the ten met at least four of the American Rheumatism Association (ARA) criteria for diagnosis of systemic lupus erythematosus. He noted that Raynaud phenomenon, loss of hair and ulcers of the mouth were more common in ANA-negative patients. It is noteworthy that these signs are all unlikely to be caused by immune complex deposition. However, only one of the ten patients had kidney involvement.

Other studies show similar findings. Pollak in 1964 obtained negative results in 9 patients among 112 with SLE. He summarized the results previously reported in seven other studies containing a total of 274 patients. He noted 7 percent of patients with negative tests for ANA. In the same year, Leonhardt reported that 3 of his 71 patients with SLE had negative tests for ANA. In 1968 Zeiman and co-workers reported clinicopathologic correlation in patients with lupus nephritis; 7 percent of their 28 patients had persistently negative tests for ANA. Estes and Christian obtained negative results in 13 percent of their 150 patients. In 1974 Bartholomew observed that 5 of 121 patients had negative ANA. In 1977 Lee and co-workers noted 5 patients with negative ANA among 110 patients followed for up to five years.

ANA-negative systemic lupus erythematosus seems to be a subgroup of SLE that has not previously been given adequate attention. Raynaud phenomenon, excessive loss of hair and ulcers of the mouth are frequent in this subgroup and the patients are noted to have had prolonged survival. Whether the ANA reaction is negative because of absent production of ANA, because of their in vivo binding by tissues or because of their being hidden in circulating immune complexes, warrants further study. In the meantime, it is important that clinicians be aware that approximately 5 percent of patients with SLE may have persistently negative tests for ANA.

DOROTHY J. BUCKNER, MD

REFERENCES

Fessel WJ: ANA-negative systemic lupus erythematosus. Am J Med 64:80-86, Jan 1978

Cohen AS, Reynolds WE, Franklin EC, et al: Preliminary criteria for the classification of systemic lupus erythematosus. Bull Rheum Dis 21:643-648, 1969

Wolf L, Sheahan M, McCormick J, et al: Classification criteria for systemic lupus erythematosus—Frequency in normal patients. JAMA 236:1497-1499, Sep 27, 1976

Provost TT: Subsets in systemic lupus erythematosus. J Invest Dermatol 72:110-113, Mar 1979

New Pustular Dermatoses of Infants

TWO NEW FORMS of cutaneous eruptions with unknown causes have been described recently in infants.

Infantile acropustulosis is an uncommon syndrome that consists of recurrent crops of pruritic papulopustules and papulovesicles 1 to 2 mm in size occurring on the distal extremities. Although this dermatosis may be present in infants at birth, it generally begins between the ages of 2 and 10 months, and may persist for two to three years before spontaneous remission occurs. This condition predominates in black infants, and there is no family history of atopy or psoriasis.

The primary lesion is a pinpoint erythematous papule which enlarges to a well-circumscribed and discrete pustule or vesicle within 24 hours. There is no tendency to coalesce. New crops of intensely pruritic vesicopustules appear for a week to ten days, then remit for an interval of two to three weeks before recurring. Most of the lesions are distributed on the palms and soles, with lesser numbers on the dorsa of the hands, wrists, feet and ankles. The eruption is said to be worse in the summer.

Histological examination of infantile acropustulosis shows nonspecific subcorneal or intraepidermal vesicles and pustules which are filled with neutrophilic polymorphonuclear leukocytes and rare eosinophils. Results of routine laboratory

examination, cultures and immunofluorescence are negative.

Infantile acropustulosis follows an intractable course and is generally unresponsive to topical steroids. Soporific doses of antihistamines are required for symptomatic relief of pruritus.

In contrast to infantile acropustulosis is the more common and benign transient neonatal pustular melanosis. The latter is typified by its invariable onset at birth, pigmented macules, vesicopustules and brief, self-limited asymptomatic course.

Transient neonatal pustular melanosis has been estimated to occur in 4.4 percent of black infants and 0.6 percent of white infants, with equal sex distribution. Neonates present at full-term with flaccid, easily ruptured pustules, measuring 3 to 5 mm in size. The pustules are not surrounded by erythema, and are found in conjunction with the more numerous hyperpigmented macules. The vesicopustules routinely rupture and resolve in 24 to 72 hours, while the pigmented macules fade in three weeks to three months. Of note is the observation that ruptured vesicopustules have a characteristic collarette of scale that surrounds a central, pigmented macule. Areas of predilection for these lesions are the chin, forehead, nape of the neck, lower back and pretibial regions. Rarely, vesicles are found on the scalp, palms and soles.

Biopsy specimens of the hyperpigmented freckles, interestingly, show only basketweave hyperkeratosis and focal basilar hyperpigmentation and lack the usual histological features of postinflammatory hyperpigmentation. Examination of vesicopustules shows intracorneal and subcorneal pustules filled with polymorphonuclear leukocytes and only sparse numbers of eosinophils. Other laboratory investigations to find a cause for this disorder have been unsuccessful.

As transient neonatal pustular melanosis is benign and self-limited in nature, no therapy is necessary.

The differential diagnosis of the two diseases discussed above should include toxic erythema of the newborn, impetigo, scabies, pompholyx, congenital cutaneous candidiasis, subcorneal pustular dermatosis and pustular psoriasis.

DAVID A. SOUTH, MD

REFERENCES

Kahn G, Rywlin AM: Acropustulosis of infancy. Arch Dermatol 115:831-833, Jul 1979

Jarratt M, Ramsdell W: Infantile acropustulosis. Arch Dermatol 115:834-836, Jul 1979

Wyre HW Jr, Murphy MO: Transient neonatal pustular melanosis. Arch Dermatol 115:458, Apr 1979

Practical Advances in Immunohistology

IMMUNOHISTOLOGIC STAINING TECHNIQUES are frequently used in dermatopathology as an adjunct to routine histopathology in the diagnostic evaluation of several dermatologic diseases. For several years direct immunofluorescence and, occasionally, immunoperoxidase staining methods have been used to identify depositions of immunoglobulins and complement in unfixed (Michel's holding solution or quick frozen) sections of skin. The ability to carry out such staining procedures is integral to confirming a histopathologic diagnosis of discoid and systemic lupus erythematosus, bullous pemphigoid, pemphigus vulgaris, pemphigus foliaceus, pemphigus erythematosus, dermatitis herpetiformis and herpes gestationis.

Attempts to adapt immunofluorescence staining to formalin-fixed and paraffin-embedded tissue sections have had limited success. Formalin fixation causes not only diminution of antigenicity when compared with unfixed preparations but also increased autofluorescence of various tissue elements. Because these fixation alterations reduce the sensitivity of immunofluorescence, an assumption had existed that immunohistologic staining methods could not be practically applied to formalin-fixed tissue sections.

In recent years, highly sensitive immunoenzyme staining techniques using horseradish peroxidase-labeled antibodies, have been successfully employed to localize antigens in both unfixed and formalin-fixed tissues. In contrast to immunofluorescence, immunoperoxidase-stained preparations offer the additional advantage of being permanent and can be counter-stained with routine histochemical stains. They can also be examined with routine light microscopy and can be adapted for electron microscopy.

Antigens which have been stained by immunoperoxidase methods comprise various immunoglobulins, hormones, enzymes, components of neuroendocrine cells, tumor markers and infectious agents. Some of the organisms which have been localized by immunoperoxidase techniques include *Treponema pallidum, Sporotrix schenckii* and *Cryptococcus neoformans,* hepatitis B antigen, herpes simplex and other viruses, and *Entamoeba histolytica.* The recent identification of specific cell surface antigens of human T and B lymphocytes has allowed the characterization of

both inflammatory and malignant lymphocytic infiltrates by immunoperoxidase staining methods.

Immunoperoxidase staining offers new practical applications to the histopathologist. Antigens which previously were difficult or impossible to visualize with routine histochemical stains can now potentially be localized by immunoperoxidase techniques in either unfixed or formalin-fixed tissue sections with routine light microscopy. Because immunoperoxidase methods are relatively simple and lend themselves to a lyophilized kit form, such procedures could easily be used in pathology laboratories in local hospitals.

In addition to the practical considerations of methodology, immunohistochemical procedures require the assurance of specificity, which relies on well-characterized antisera. The recently developed ability to hybridize clones of neoplastic plasma cells in cell culture with single antibody-forming cells from immunized animals provides a vast potential in the production of highly characterized monospecific antibodies. As antigenic markers of various components of normal and immunologically altered tissues, malignant cells and infectious organisms continue to be isolated, characterized, and used to produce specific antibody, immunohistologic staining methods will continue to advance our ability to better identify and understand disorders involving skin as well as other tissues.

JAMES H. BECKETT, MD

REFERENCES

Cooperative Study: Uses for immunofluorescence tests of skin and sera—Utilization of immunofluorescence in the diagnosis of bullous diseases, lupus erythematosus, and certain other dermatoses. Arch Dermatol 111:371-381, Mar 1975

Burns J, Hambridge M, Taylor CR: Intracellular immunoglobulins—A comparative study on three standard tissue processing methods using horseradish peroxidase and fluorochrome conjugates. J Clin Pathol 27:548--557, Jul 1974

New vistas in histopathology. Lancet 2:930, Oct 28, 1978

ADVISORY PANEL TO THE SECTION ON DERMATOLOGY

VICTOR D. NEWCOMER, MD
Advisory Panel Chairman
CMA Scientific Board Representative
Santa Monica

CLEVE B. BAKER, MD
CMA Section Chairman
Woodland

JOYCE NANESS FOX, MD
CMA Section Secretary
Studio City

ANTONIO LOPEZ, MD
CMA Section Assistant Secretary
La Jolla

EDWIN T. WRIGHT, MD
Loma Linda University

DAVID A. SOUTH, MD
Section Editor
Stanford University

LAURENCE BASS, MD
University of California, Davis

HELEN GOTTSCHALK, MD
University of California, Irvine

A. RAZZAQUE AHMED, MD
University of California, Los Angeles

RICHARD B. STOUGHTON, MD
University of California, San Diego

WILLIAM L. EPSTEIN, MD
University of California, San Francisco

NORMAN E. LEVAN, MD
University of Southern California
Los Angeles

A. PAUL KELLY, MD
Charles R. Drew Postgraduate Medical School
Los Angeles

MEYER BERKE, MD
Lakewood

DON R. SEIDMAN, MD
Tarzana

EDITORIALS

Deregulation and Governance in Health Care

As this issue goes to press a new Congress will have convened and a new President is about to be inaugurated. It is too early to sense what all the consequences may be. Some expect that they will be dire, and destructive of progress—social or otherwise. Others are convinced that we are on the threshold of a rejuvenated America destined to reaffirm its historic industrial, social, economic and political preeminence in an all too confused and contentious world. But all seem to share a hope or an expectation that things will somehow be different, whether for better or worse.

And there is a whiff of deregulation in the air. In all fairness it got under way during the previous administration and appears likely to continue under the new one. But whether or to what extent it can or will be applied in health care remains to be seen. Any deregulation in health care will not be easy. For more than a decade regulation of the health care enterprise by government has become increasingly institutionalized through gradual but apparently inexorable enactment and implementation of a series of federal laws which affect virtually every facet of health and health care. There are now literally hundreds of federal agencies with rules pertaining to medical education, research, patient care and other aspects of health, and the 50 states and thousands of local communities have also contributed their share of legislation and regulations. It would seem that something like a critical mass of regulation may already be in place and that any significant deregulation of health care may now be difficult indeed.

Yet some deregulation of the health care enterprise is a consummation devoutly wished by most physicians. A large number would agree that many laws and regulations, no matter how well intentioned, have turned out to create more problems than they solve and to add substantially and unproductively to health care costs. Yet some regulation or governance is clearly necessary. The problem which has yet to be solved is how an interdependent system, with autonomous and independent parts which are changing all the time, can best be governed. Fixed laws and cumbersome regulations too often are proving both inadequate and inappropriate for governance of such a dynamic, changing, really natural social system. This appears to be a seminal problem for America as a whole, as the fine structure of its natural free society becomes ever more interrelated and ever more interdependent. The problem is a fundamental one and it just happens to be coming into focus most clearly in the health care enterprise where the evidence is accumulating that fixed laws and regulations are simply too insensitive and too sluggish to be compatible with rapid progress and change as it occurs in a dynamic and, if you will, natural social system.

Perhaps there is now an opportunity to recognize that a vital system such as the health care enterprise will simply not thrive in an artificial environment of restrictive laws and regulations which are external to it. Some relief is needed from these artificial initiatives and controls which are simply not working. But anarchy or complete absence of governance or control cannot be ex-

pected to work well either. Somehow the natural interrelationships and interdependencies must come to be recognized for what they are, and then dealt with more effectively and in greater collaboration with the autonomous and independent parts within the system that must do whatever is to be done. This is a formidable challenge for a rejuvenating America, and for its health care enterprise, since this is where this fundamental problem seems first coming into sharpest focus.

To make a start it is first necessary for all concerned to recognize the problem for what it is. Then steps can be taken to disengage the health care enterprise from some of its present unnatural legal and regulatory shackles, and at the same time to develop a more natural and more sensitive governance of the system which will involve the important forces within it. Perhaps this process can begin under the new Congress and the new President. One can hope that it will.

—MSMW

Prognosis After Myocardial Infarction

PATIENTS ADMITTED to coronary care units (CCU) with acute myocardial infarction have an inhospital mortality of 15 percent to 20 percent. While this represents an improvement over the 25 percent to 30 percent mortality in the era before CCU's it is unlikely that further substantial reductions in early mortality will occur until effective therapy to limit infarct size becomes readily applicable, perhaps even in the prehospital phase of the infarction. Current areas of interest in the management of patients surviving the initial stay in hospital involve the identification of subsets of patients, who are at high, intermediate or low risk for future coronary events. With such identification, high-risk patients could be offered aggressive medical or surgical therapy while potentially dangerous treatments and investigative procedures could be avoided in low-risk patients. As Kishpaugh and her co-workers indicate in their paper elsewhere in this issue, there is an important "need for physicians to know those factors which affect long-term prognosis of patients with ischemic heart disease." Although these authors have presented little new information on how physicians can recognize these factors, their report has merit in that it reemphasizes the magnitude of the problem we face in treating such patients (nearly 40 percent mortality during the five-year follow-up period.)

A number of studies have appeared in recent years that show the reliability of easily obtained clinical data in separating high-risk from low-risk survivors of acute myocardial infarction. The patient's age, heart size on admission (or discharge), findings on x-ray films of the chest and history of previous infarction were found to be the most powerful predictors of mortality in the six-year follow-up study reported by Norris and colleagues.[1] The predictive value of the initial x-ray study of the chest alone, with attention to cardiothoracic ratio and pulmonary venous congestion, is excellent according to the recent study of Battler and co-workers.[2] These data simply indicate that the extent of damage to the left ventricle, both from the index event and from prior infarcts, is a fundamental determinant of long-term survival. More complicated and expensive tests to assess ventricular function have confirmed these findings.[3] The additional, and possibly independent, risk factor of ventricular ectopy detected by 6- to 24-hour ambulatory electrocardiography has also received considerable attention, beginning with the initial reports from the Coronary Drug Project.[4,5] Combining the two factors of pronounced left ventricular damage and late hospital-phase arrhythmias, one can separate accurately the high-risk from the low-risk patients.[6,7] Even coronary angiography and left ventriculography, though obviously the gold standards for assessing prognosis in ischemic heart disease, do not seem to provide additional, clinically useful information.[8]

Within the group of patients having no late arrhythmias in hospital and minimally damaged ventricles, there are some who remain at excessive risk of recurrent ischemic events. Low-level treadmill exercise testing, done as early as two weeks after the acute infarction, gives promise of identifying these patients.[9-14]

Kishpaugh and her colleagues have shown the continuing high mortality in survivors of the acute phase of myocardial infarction in the era of coronary care units, and the studies cited above have pointed the way towards a reasoned therapeutic approach to the various subgroups of patients who comprise these mortality data.

The challenge that remains is to prove the efficacy of therapy currently available and widely used.

STEPHEN C. ACHUFF, MD
Associate Professor of Medicine
Director of Clinical Programs
The Johns Hopkins University
School of Medicine, Baltimore

REFERENCES

1. Norris RM, Caughey DE, Mercer CJ, et al: Prognosis after myocardial infarction: Six year follow-up. Br Heart J 36:786-790, 1974

2. Battler A, Karliner JS, Higgins CB, et al: The initial chest x-ray in acute myocardial infarction—Prediction of early and late mortality and survival. Circulation 61:1004-1009, 1980

3. Borer JS, Rosing DS, Miller RH, et al: Natural history of left ventricular function during 1 year after acute myocardial infarction. Am J Cardiol 46:1-12, 1980

4. Kotter MN, Tabatznik B, Mower MM, et al: Prognostic significance of ventricular ectopic beats with respect to sudden death in the late postinfarction period. Circulation 47:959-966, 1973

5. Vismara LA, Amsterdam EA, Mason DT: Relation of ventricular arrhythmias in the late hospital phase of acute myocardial infarction to sudden death after hospital discharge. Am J Med 59:6-12, 1975

6. Schulze RA, Strauss HW, Pitt B: Sudden death in the year following myocardial infarction: Relation to ventricular premature contractions in the late hospital phase and left ventricular ejection fraction. Am J Med 62:92-99, 1977

7. Moss AJ, DeCamilla J, Davis H: Cardiac death in the first 6 months after myocardial infarction: Potential for mortality reduction in the early posthospital period. Am J Cardiol 39:816-821, 1977

8. Taylor GJ, Humphries JO, Mellits ED, et al: Predictors of clinical course, coronary anatomy and left ventricular function after recovery from acute myocardial infarction. Circulation 62:960-970, 1980

9. Markiewicz W, Houston N, Debusk RF: Exercise testing soon after myocardial infarction. Circulation 56:26-31, 1977

10. Smith JW, Dennis CA, Gassmann A, et al: Exercise testing three weeks after myocardial infarction. Chest 75:12-16, 1979

11. Theroux P, Waters DD, Halphen C, et al: Prognostic value of exercise testing soon after myocardial infarction. N Engl J Med 301:341-345, 1979

12. Turner JD, Schwartz KM, Logic JR, et al: Detection of residual jeopardized myocardium 3 weeks after myocardial infarction by exercise testing with thallium-201 myocardial scintigraphy. Circulation 61:729-737, 1980

13. Stein RA, Walsh W, Frank F, et al: Clinical value of early exercise testing after myocardial infarction. Arch Intern Med 140: 1178-1181, 1980

14. Koppes GM, Kruyer W, Beckmann CH, et al: Response to exercise early after uncomplicated acute myocardial infarction in patients receiving no medication: Long-term follow-up. Am J Cardiol 46:764-769, 1980

It's Not Just How Low You Make It, but How You Make It Low

IN THE MAIN, acute severe hypophosphatemia induces dysfunction in organs whose tissue stores of inorganic phosphate (P_i) are already seriously depleted. One mechanism by which acute severe hypophosphatemia can induce organ dysfunction is by so severely depleting cellular stores of P_i that cellular P_i becomes determining of both the concentration and rate of regeneration of adenosine triphosphate (ATP). When severe, depletion of cytoplasmic P_i can restrict both anaerobic and aerobic *regeneration* of ATP from adenosine diphosphate (ADP) and P_i. Also, in the liver and renal cortex, depletion of P_i can increase the rate at which cytoplasmic adenosine monophosphate (AMP) is deaminated to inosine monophosphate (IMP). Because the adenine nucleotides ATP, ADP and AMP are in equilibrium in the cytoplasm of all cells, and because the deamination of AMP enhanced by cytoplasmic depletion of P_i (by deinhibiting cytoplasmic AMP deaminase) is irreversible, acute severe cytoplasmic depletion of P_i in the liver and renal cortex can induce in these tissues severe reductions in the *concentration* of total adenine nucleotides and in particular that of ATP.

As emphasized by Dr. James Knochel in his interesting and eminently useful review of hypophosphatemia elsewhere in this issue, ATP is the most important energetic currency of the cell, and one might predict that a severe reduction of either the cellular concentration or regeneration of ATP could give rise to disorders of cell function and structure. In fact, in clinical states of severe hypophosphatemia, severe reductions of P_i and ATP have been documented in the erythrocyte, leukocyte, platelet and somatic muscle, and therapeutic replenishment of depleted P_i can be attended by reestablishment of biochemical and functional integrity of these tissues. In particular, in hypophosphatemic chronic alcoholic patients and in patients rendered hypophosphatemic by excessive ingestion of antacid, severe depletion of P_i predictably occurs in somatic muscle and sometimes in the myocardium, and the depletion can cause a clinically important functional disorder that can be corrected with therapeutic replenishment of P_i.

Yet, the indications for phosphate therapy remain unclear. As pointed out by Dr. Knochel, intravenous administration of phosphate is not without risk. It has been known for many years that severe hypophosphatemia often occurs during treatment of diabetic ketoacidosis with insulin. In this setting, clear-cut biochemical and physiological abnormalities of leukocytes and erythrocytes have been shown. There is no persuasive evidence, however, that administering phosphate to prevent or correct the hypophosphatemia reduces either the morbidity or mortality of diabetic ketoacidosis. *Anabolism* has often been invoked to explain the occurrence of hypophosphatemia during (1) treatment of patients with diabetic ketoacidosis, (2) withdrawal of alcohol in alcoholic persons and (3) the initial period of feeding or hyperalimen-

tation in malnourished patients. In fact, relatively little is known of the details of such evident accumulation of tissue phosphate in any of these acutely hypophosphatemic conditions. Even when phosphate therapy is not given to patients with diabetic ketoacidosis, the severity of their hypophosphatemia characteristically moderates shortly after diabetic ketoacidosis is corrected. Thus, in patients with this disturbance, the acute severe hypophosphatemia that attends its initial treatment reflects a metabolic disorder different from that reflected by the persisting hypophosphatemia of patients with chronic alcoholism who are withdrawing from alcohol. It is important then to distinguish between the capacity of acute severe hypophosphatemia to induce metabolic and physiological disorder and the likelihood that hypophosphatemia in a given clinical setting reflects a disorder that should be treated with phosphate.

It should not be inferred that only severe hypophosphatemia induces or reflects metabolic disorders that will respond favorably to phosphate therapy. Specifically, it cannot be assumed that (1) only severe hypophosphatemia can induce, or reflect, a depletion of tissue P_i severe enough to cause a clinically important metabolic or physiologic disturbance or (2) that the pathogenetic mechanism of a hypophosphatemic metabolic disorder that can respond to phosphate therapy necessarily depends on severe depletion of cellular P_i. For example, if even moderately severe hypophosphatemia is present at the outset of diabetic ketoacidosis, the hypophosphatemia probably reflects very severe depletion of tissue stores of phosphate, and phosphate should be administered. The characteristically explosive hypophosphatemic syndrome of disturbed mentation that is often associated with paresthesias can respond dramatically to phosphate therapy, even when hypophosphatemia is not severe.

Severe intracellular depletion of phosphate with only minimal to moderate hypophosphatemia is predictably induced by the intravenous administration of certain sugars that are very rapidly phosphorylated in certain tissues. One of these sugars, fructose, is still rather widely used clinically. Sorbitol, which is converted to fructose in the liver (and presumably in the renal cortex as well), xylitol, glycerol and mannose are, like fructose, caloric substances which can induce severe intracellular depletion of P_i and substantial reductions of ATP and total adenine nucleotides in the liver and renal cortex. Fructose and xylitol have been marketed for intravenous administration and claimed to have special nutritional advantages. In this country, intravenously administered fructose and invert sugar (the 1:1 fructose/glucose product of the hydrolysis by invertase of sucrose) are used in the treatment of diabetic ketoacidosis and as a source of calories postoperatively. There would appear to be no compelling clinical indications for intravenously administered fructose, xylitol, glycerol or sorbitol. All of these sugars are potentially dangerous because their intravenous administration can induce severe tissue depletion of P_i, the above stated metabolic consequences and, in the case of fructose, severe lactic acidosis as well.[1] It is apparent that intravenous administration of these sugars might be fraught with particular risk in those clinical conditions in which severe tissue depletion of phosphate already exists.

The quintessential instance of incisive depletion of tissue phosphate is that depletion induced in patients with hereditary fructose intolerance (HFI), when these patients are exposed to fructose in even small amounts. In this instance, genetically deficient aldolase "B" in the liver, renal cortex and epithelium of the small bowel dictates these tissues' accumulation of fructose-1-phosphate in great amounts and consequent severe cellular depletion of phosphate.[2] Inadvertently, a number of patients with HFI have been severely fructose intoxicated in a hospital setting. One of these patients, a 12-year-old boy with known HFI, died as a direct and near immediate consequence of his intravenous receipt of invert sugar in the postoperative state; it was not appreciated that fructose comprises half of invert sugar. This patient had extremely severe hyperchloremic acidosis, hypophosphatemia and acute renal failure (without antecedent hypotension or evidence of renal disease).

In patients with HFI, the intravenous administration of fructose induces a dose-dependent complex dysfunction of the renal tubule with the features of Fanconi syndrome and type II "proximal" renal tubule acidosis.[3] The renal dysfunction occurs in combination with a dose-dependent hypophosphatemia and hyperuricemia, neither of which is caused by the renal dysfunction. The hyperuricemia is the consequence of degradation of preformed adenine nucleotides. By activating cytoplasmic AMP deaminase, the fructose-induced depletion of P_i enhances the irreversible deamination of AMP to IMP, a precursor of uric acid via the sequence, inosine, hypoxanthine, xanthine.[4]

Both the renal dysfunction and the hyperuricemia can be induced by fructose in amounts that cause no symptoms and induce only modest hypophosphatemia. Yet, the renal dysfunction and hyperuricemia, and the increased urinary excretion of inosine, hypoxanthine and xanthine experimentally induced by fructose, are strikingly attenuated by prior intravenous loading with phosphate.[5] In patients with HFI, Mock and his associates have recently found that an experimental relaxation of fructose restriction that did not give rise to symptoms did induce within three days persisting hyperuricemia, hyperuriocosuria and transient hypophosphatemia demonstrable only in the postprandial period.[6] One could predict that the hyperuricemia-hyperuricosuria of this circumstance could be attenuated by increased dietary intake of phosphate. It is of interest in this regard that many adult patients as well as children with HFI continually drink rather large amounts of milk. Milk provides not only nonfructose sugar but also substantial amounts of phosphate, as noted by Dr. Knochel.

Glorieux and his colleagues have shown that in children with hypophosphatemic rickets, somatic growth is enhanced and metabolic bone disease prevented or mitigated when phosphate is administered on a continuing basis in combination with vitamin D.[7] These observations provide, perhaps, the best evidence that chronic phosphate therapy can be greatly beneficial in a disease characterized by chronic, moderately severe hypophosphatemia.

One can predict the identification of disease states in which even normal concentrations of P_i in the cytoplasm will not enable (1) rates of P_i transport across the mitochondrial membrane sufficient to underwrite normal rates of regeneration of ATP or (2) normal (physiological) supression of AMP deaminase. One can envision a mitochondrial membrane disordered such that a phosphate transport mechanism has a reduced affinity or capacity for P_i. In brush border membrane vesicles prepared from the kidneys of X-linked hypophosphatemic mice, Scriver and his associates have recently reported an apparently isolated impairment of phosphate transport.[8] In the renal tubule, impaired transport of P_i by the mitochondrial membrane might be predicted to give rise to a complex derangement of energy-requiring transepithelial transport function. In this regard, it is of interest that Al-Bander and his colleagues have recently shown that phosphate loading strikingly attenuates the Fanconi-like complex dysfunction of the proximal renal tubule induced by maleic acid in dogs.[9]

One can envision a disorder of the renal tubule in which cytoplasmic P_i fails to suppress AMP deaminase. The basis of such failed suppression could be of two general kinds: either the enzyme itself is abnormal in a way that precludes its suppression by normal concentrations of cytoplasmic P_i or the renal tubule cannot maintain normal concentrations of P_i in that part (or compartment) of the cytoplasm that contains the enzyme. In view of the evidence that in rats and chickens a substantial amount of the uric acid excreted in urine is produced in the kidney,[10] the occurrence of hyperuricosuria in humans, particularly in the absence of hyperuricemia, could reflect an impairment of P_i-dampening of renal AMP deaminase. If in such a disorder the cytoplasmic concentration of P_i in the renal tubule can be increased by phosphate therapy, the severity of nephrogenic hyperuricosuria might be reduced by phosphate therapy. In fructose-loaded rats, prior loading with phosphate prevents the otherwise substantial reduction in concentrations of total adenine nucleotides in the renal cortex, but only modestly attenuates this reduction in the liver.[11] Because the activity of AMP deaminase in the renal cortex appears to reflect the same isoenzyme as that in the liver, the differential attenuating effect of phosphate loading could reflect the presumed greater access of administered phosphate to the cytoplasm of cells of the renal cortical tubules, owing to their high-affinity, high-capacity transepithelial transport process for phosphate.[11] Several lines of evidence support the proposition that hyperuricosuria is a critical determinant of the formation not only of uric acid kidney stones but also of that majority of kidney stones principally containing calcium oxalate.[12] The demonstrated effectiveness of allopurinol in reducing the severity of hyperuricosuria and the clinical frequency of nephrolithiasis[12] may depend in part on the drugs suppressing the renal production of uric acid.[10] There is some evidence that phosphate therapy is effective in reducing the clinical frequency of nephrolithiasis. It will be of considerable interest to determine whether phosphate therapy is most effective in those patients in whom it reduces the severity of hyperuricosuria and inosinuria.

It seems likely that in the next few years many clinically important dysphosphatotic conditions will be described. It also seems likely that a num-

ber of such conditions will not be characterized by hypophosphatemia. There is reason to be hopeful that careful clinical and biochemical definitions of these anticipated conditions will enable many of those affected to be successfully treated.

R. CURTIS MORRIS, Jr., MD
Director of General Research Center
University of California, San Francisco

REFERENCES

1. Woods HF, Alberti KGMM: Dangers of intravenous fructose. Lancet 2:1354-1357, Dec 23, 1972

2. Froesch ER: Essential fructosuria and hereditary fructose intolerance, *In* Stanbury JB, Wyngaarden JB, Fredrickson DS (Eds): The Metabolic Basis of Inherited Disease, 3rd Ed. New York, McGraw-Hill Book Co, 1972, pp 131-148

3. Morris RC Jr: An experimental renal acidification defect in patients with hereditary fructose intolerance—II. Its distinction from classic renal tubular acidosis: Its resemblance to the renal acidification defect associated with the Fanconi syndrome of children with cystinosis. J Clin Invest 47:1648-1663, 1968

4. Maenpaa PH, Ravio KO, Kekomaki MP: Liver adenine nucleotides: Fructose-induced depletion of its effect on protein synthesis. Science 161:1253-1254, 1968

5. Morris RC, Brewer ED, Brater C: Evidence of a severe phosphate-depletion-dependent disturbance of cellular metabolism in patients with hereditary fructose intolerance (HFI), abstracted. Clin Res 28:566a, 1980

6. Mock DM, Tsai H, Perman JA, et al: Chronic fructose intoxication in apparently asymptomatic patients with hereditary fructose intolerance (HFI), abstracted. Clin Res, 1981 (In Press)

7. Glorieux FH, Scriver CR, Reade TM, et al: Use of phosphate and vitamin D to prevent dwarfism and rickets in X-linked hypophosphatemia. N Engl J Med 287:481-487, 1972

8. Tenenhouse HS, Scriver CR, McInnes RR, et al: Renal handling of phosphate *in vivo* and *in vitro* by the X-linked hypophosphatemic male mouse: Evidence for a defect in the brush border membrane. Kidney Intl 14:236-244, 1978

9. Al-Bander H, Mock DM, Paukert T, et al: Phosphate loading attenuates the severity of the renal tubular disorder induced by maleic acid (MA) in the dog, abstracted. Clin Res, 1981 (In Press)

10. Chin TY, Cacini W, Zmuda MJ, et al: Quantification of renal uric acid synthesis in the rat. Am J Physiol 238:F481-F487, 1980

11. Morris RC Jr, Nigon K, Reed EB: Evidence that the severity of depletion of inorganic phosphate determines the severity of the disturbance of adenine nucleotide metabolism in the liver and renal cortex of the fructose-loaded rat. J Clin Inves 61:209-220, 1978

12. Coe FL: Nephrolithiasis—Pathogenesis and Treatment. Chicago, Year Book Medical Publishers, 1978, pp 1-235

Physicians' Fees—Not Too Bad a Record

A RECENT COMMUNICATION in the *Journal of the American Medical Association* by G. L. Glandon and J. R. Werner[1] reviews physicians' practice experience in the decade of the 1970's. Data were collected by the AMA Center for Health Services Research and Development in 1970 and 1980, with particular attention to average incomes, expenses and fees. These are considered in relation to the real gross national product, which declined in the 1970's, and the cost of living, which doubled.

While physicians' net incomes are projected to have increased from $41,800 in 1970 to $80,000 by the end of 1980, their real income in uninflated dollars changed little if at all. Practice expenses rose from $24,300 in 1970 to a projected $54,500 in 1980. As gross income increased practice expenses rose commensurately.

During the 1970's physicians' fees were the subject of considerable attention and criticism by government and others. However, the facts appear to show that the real income of physicians did not rise and in fact remained essentially unchanged. This is not too bad a record.

—MSMW

REFERENCE

1. Glandon GL, Werner JL: Physicians' practice experience during the decade of the 1970s (Special Communication). JAMA 244:2514-2518, Dec. 5, 1980

CASE REPORTS

Refer to: Hoffman JR, McElroy CR: Bicarbonate therapy for dysrhythmia and hypotension in tricyclic antidepressant overdose. West J Med 134:60-64, Jan 1981

Bicarbonate Therapy for Dysrhythmia and Hypotension in Tricyclic Antidepressant Overdose

JEROME R. HOFFMAN, MD
CHARLES R. McELROY, MD
Los Angeles

SUICIDE IS THE fourth leading cause of death in persons 5 to 40 years of age in the United States.[1] Unfortunately, people attempting suicide with tricyclic antidepressants are often successful.[2-4] These drugs are prescribed largely for persons suffering depression. They have a delayed onset of maximal therapeutic effect, thus allowing time for persons still in a depressed state to take a suicidal overdose before the desired mood elevation supravenes. Tricyclic drugs have devastating pharmacological effects on the heart, as well as on the brain, gastrointestinal tract and neurovascular system.[4-28] While the potentially life-threatening dysrhythmias associated with tricyclic drug overdose are well known, the value of alkalinization therapy has been appreciated only recently.[29-34] We present a case that dramatically demonstrates the effectiveness of such therapy for treating tricyclic drug overdose.

Report of a Case

The patient was a 25-year-old woman transferred to the UCLA (University of California, Los Angeles) Emergency Medicine Center from a local hospital with a presumptive diagnosis of overdose with unknown medications. The patient had a history of six previous suicide attempts, five times with drug overdose and once with a self-inflicted gunshot wound. At the time of admission she was being treated at the UCLA Neuropsychiatric Institute for depression, and was on a therapeutic regimen of imipramine (Tofranil). She had left her house at 2:00 AM on the morning of her admission, and when she returned four hours later, her mother found her to be mumbling incoherently. She was taken to a local emergency room where she was noted to be combative and incoherent. She was treated with gastric lavage, magnesium citrate and activated charcoal and was transferred to the UCLA Emergency Medicine Center.

On arrival, the patient exhibited bizarre behavior, alternately screaming paraphrasically and swinging her arms and legs violently and then lying very still. She was placed in a quiet room and the lights were turned down, at which time she lay still on her bed. However, whenever any sensory input was provided, she began to scream and rage again. Further examination showed sluggishly reactive dilated pupils and bidirectional nystagmus. Examination showed that her chest, heart and abdomen were all normal with the exception of a regular tachycardia. Her neurological examination was entirely within normal limits with the exception of the mental status decribed above. Her skin was dry and warm.

An electrocardiogram (EKG) taken at the time of admission to the Emergency Medicine Center detected a tachycardia with wide bizarre QRS complexes (Figure 1). The underlying rhythm appeared to be regular but had occasional apparently premature complexes. At this time the patient's blood pressure was 90/50 mm of mercury. Arterial blood gas measurements showed a pH of 7.29 and a carbon dioxide tension (Pco_2) of 29 mm of mercury and intravenous alkalinization therapy was instituted with 88 mEq of sodium bicarbonate. The patient's QRS complexes narrowed towards normal almost immediately, and the QRS duration became 0.12 seconds. The rhythm became clearly regular (Figure 2). A second blood gas determination was made, which showed a pH of 7.40 and Pco_2 of 35 mm of mercury. At this time the patient's blood pressure

From the Department of Medicine, Division of Emergency Medicine, University of California, Los Angeles, Center for the Health Sciences.

Submitted, revised, February 11, 1980.

Reprint requests to: Jerome R. Hoffman, MD, Emergency Medicine Center, UCLA Hospital and Clinics, Center for the Health Sciences, 10833 Le Conte, Los Angeles, CA 90024.

was 110/70 mm of mercury and her pulse rate remained 108 per minute. She was given a third ampule of 44 mEq of sodium bicarbonate, and her EKG again showed dramatic narrowing of her QRS complexes to within normal limits (Figure 3). A third blood gas determination was done, which showed a pH of 7.47 and a P_{CO_2} of 34.5 of mercury. The patient's blood pressure was stable at 130/90 mm of mercury and her pulse was 84 per minute and regular. She was admitted to the coronary care unit (CCU) for observation and monitoring.

The patient's hospital course was entirely unremarkable. At no time during her stay in the CCU

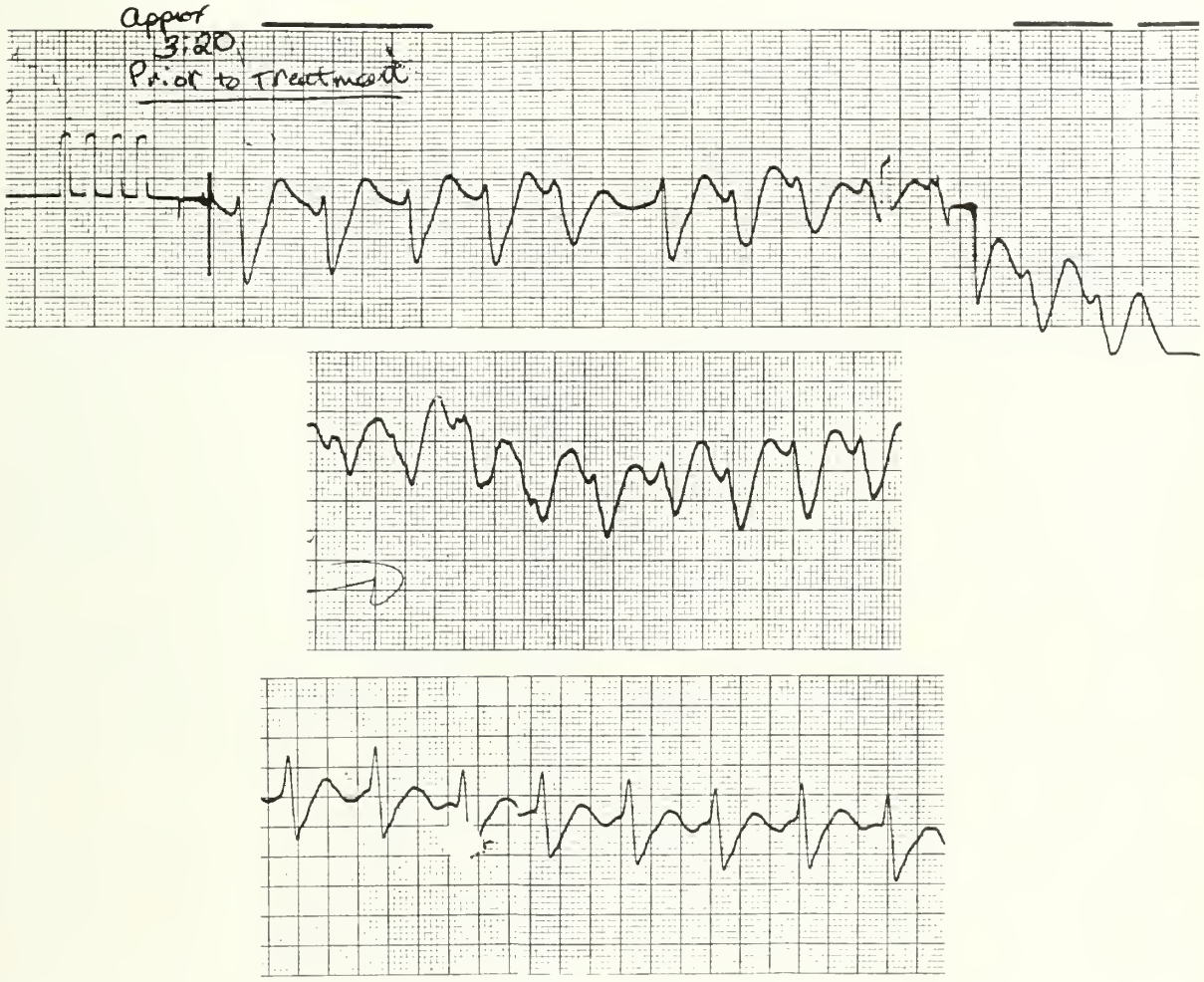


Figure 1.—Regular tachycardia with wide, bizarre QRS complexes, associated with systemic hypotension and arterial pH of 7.29.

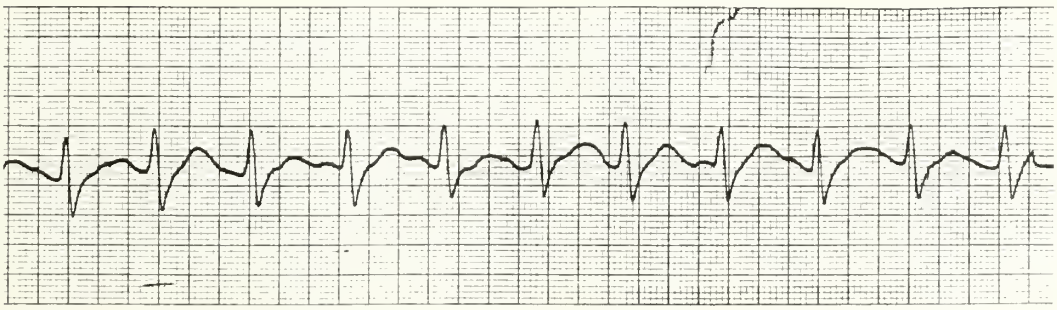


Figure 2.—Regular tachycardia with QRS of 0.12 seconds duration, following initial bicarbonate therapy that resulted in arterial pH of 7.40.

did she show any cardiac dysrhythmias, and at no time did she have prolongation of her QRS complexes. A urine drug screen showed the presence of salicylate and imipramine, as well as qualitatively but not quantitatively detectable amounts of barbiturate and diazepam. The level of imipramine in the patient's blood at admission was 1,000 ng per ml. All of the laboratory test results (including electrolytes and complete blood count, liver function, renal function, calcium and magnesium) were within normal limits. The patient's mental state became stable during the first 24 hours, and she was discharged after psychiatric consultation during which psychiatric follow-up was recommended.

Discussion

Our patient's acute psychosis was strongly suggestive of either phencyclidine or scopolamine overdose, although neither of these drugs was found in the patient's blood or urine. However, the test for urine salicylate was positive. Scopolamine is often difficult to identify in drug overdose, but it is frequently suggested by the presence of salicylamide with which it is combined in numerous preparations. While we cannot be certain that this was the basis for the patient's acute psychotic behavior, we suspect that this may well have been the case.

The initial rhythm of the patient's heart was, in retrospect, most likely a supraventricular tachycardia with widened QRS complexes secondary to direct tricyclic toxicity, with occasional premature ventricular contractions. An initial consideration of ventricular tachycardia, suggested in part by the hypotension, appears quite unlikely, particularly in light of the response seen with therapy.

Clinical guidelines are generally used to recognize serious tricyclic antidepressant overdose.[35] However, while toxic effects, including even fatal dysrhythmias, may occur with routine doses and "normal" levels of the drug in the blood,[4,8,9,30,35] there is some evidence to suggest that the degree of toxicity increases in proportion to increases in levels of the drug in the blood, and that blood levels equal to or greater than 1,000 ng per ml in particular put the patient at a much higher risk for dysrhythmias, conduction abnormalities, seizures and cardiac arrest.[31,36-38] It has also been observed that blood levels of greater than 1,000 ng per ml likewise correlate with QRS durations of greater than 0.10 seconds.[36]

Following a review of 254 tricyclic drug overdoses, investigators from the Colorado Poison Control Center made two important observations: (1) The latest onset of dysrhythmia occurred 19 hours after admission and (2) a tachycardia of 110 or more per minute was associated with a risk of subsequent dysrhythmia and was considered to require 24 hours of monitoring. Their criteria for treating tricyclic overdoses were (1) if dysrhythmia was present on admission, the patient was considered to require 24 hours of monitoring and (2) any dysrhythmia present after the time of admission was considered to require 24 hours of monitoring from that time.[39]

The above are useful criteria, although we have seen a case at UCLA in which potentially life-threatening dysrhythmia first occurred 36 hours following admission. The literature also includes numerous isolated reports of late cardiac deaths.[25,26,40-42]

The most significant cardiac manifestations of tricyclic drug overdose are dysrhythmia and hypotension. The hypotension associated with such an overdose can be difficult to manage, both because of its poor response to pressor agents and because of theoretical objections to the use of pressors in this circumstance.[5,6,31] The cardiovas-

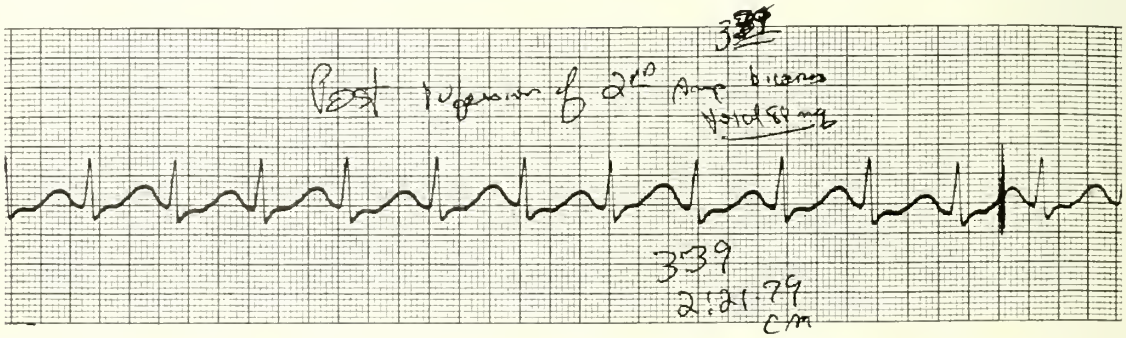


Figure 3.—Supraventricular tachycardia with normal QRS, associated with normotension and arterial pH of 7.47, following subsequent bicarbonate therapy.

cular system in the presence of tricyclic antidepressant overdose may well show increased sensitivity to catecholamines.[43-51] Because the amine pump has been blocked, there is bioamine depletion at the neuroeffector sites, but there is also nonhomogeneous pharmacological activity that can then sensitize the person to a nonuniform response to exogenous catecholamines. Vasopressors may also enhance ectopic dysrhythmic activity, further complicating an already difficult situation. It is for this reason that the general initial treatment for hypotension should be intravenous infusion of fluid.[5,6,31] If the hypotension does not respond to simple volume expansion, management of arterial pH with alkalinization therapy will often be successful in reversing hypotension. Brown and others have reported that alkalinization of patients with tricyclic drug overdose to pH's of 7.50 to 7.55 is routinely accompanied by a reversal of hypotension.[29-37] This is explained on the basis of changes in tricyclic protein binding, which then makes these agents less available to the tissues and reduces their toxic effect.[52-54]

The value of alkalinization in tricyclic antidepressant overdose may well have a precedent in the efficacy of such therapy in cases of quinidine overdose. Quinidine has effects on cardiac electrical activity similar to those of tricyclic antidepressants.[56-58] This is true at both therapeutic and toxic levels. These include, most notably, prolongation of PR interval and rate-corrected QTc interval, and progressive broadening of the QRS complex.[55-60] Furthermore, quinidine toxicity can produce hypotension, cardiac dysrhythmias and metabolic acidosis.[57-60] Alkalinization therapy has been advocated with quinidine overdose to decrease serum drug levels by increasing protein binding, as well as to lower serum potassium (because increased potassium levels are associated with increased toxicity) and increase urinary excretion.[58-63]

The use of physostigmine, often enthusiastically recommended for the treatment of both hypotension and dysrhythmia, has failed to show consistently a reversal of hypotension.[5,32,39,64-68] It may, however, play an important role in treating patients who remain hypotensive after both volume expansion and alkalinization.

Various pharmacological agents have been used to treat tricyclic-induced cardiac dysrhythmias. Physostigmine has generated much interest but is a less than optimal therapeutic drug for several reasons. Most important is that it is not uniformly successful. It also can cause such severe side effects as seizures, hyperperistalsis, hypersalivation and bradycardia.[5,32,39,64-68] Finally, it produces an increase in vagal tone, which theoretically could increase the degree of heart block in severe cases.

Lidocaine would appear to work in theory because it increases, or at worst has no effect on, the speed of atrioventricular conduction. However, it has met with limited clinical success. Furthermore, it may potentiate the hypotensive effect of the tricyclic drugs.[2,32,69] Diaphenylhydantoin similarly makes theoretical sense, but has been shown to work poorly, if at all, in the treatment of tricyclic antidepressant overdose.[32] Propranolol is contraindicated because of its potent negative inotropic effect, as well as its tendency to increase heart block.[2,32]

Despite the availability of numerous antidysrhythmic drugs, there is no current consensus concerning the best therapeutic regimen. There may be, nevertheless, a possible unifying concept allowing a rational approach to both hypotension and cardiac dysrhythmias secondary to tricyclic drug overdose. In most patients suffering from shock and dysrhythmias pronounced acidosis occurs. In the case of tricyclic-induced overdose, it is generally a combined metabolic and respiratory acidosis. As pH falls, more drug may become unbound from serum proteins and, hence, be available to tissues for biologic activity. Thus, a vicious circle occurs. Various investigators have reported great success in managing both the hypotension and cardiac dysrhythmias associated with tricyclic drug overdose through alkalinization therapy. This should be combined with optimal ventilation to produce a P_{CO_2} of approximately 40 mm of mercury, as well as supplemental oxygen to reduce any concomitant tissue hypoxia, along with the administration of bicarbonate to bring arterial pH to between 7.50 and 7.55. As our case dramatically shows, this will often obviate the need to use physostigmine—a drug with significant morbidity—or other agents.

Conclusion

Tricyclic antidepressant overdoses are often associated with life-threatening hypotension and cardiac dysrhythmias. We present a patient with tricyclic drug overdose accompanied by an unusual tachycardia with wide, bizarre QRS complexes and associated hypotension who responded dramatically to alkalinization therapy. We believe

that along with volume expansion, as necessary, alkalinization should be the therapy of first choice for hypotension and dysrhythmia secondary to tricyclic antidepressant overdose.

REFERENCES

1. Facts of Life and Death, Publication No. (PHS) 79-1222, US Dept of Health, Education and Welfare, Nov 1978, pp 39-47
2. Byck R: Chap 12, *In* Goodman LS, Gilman A (Eds): Pharmacological Basis of Therapeutics. 5th Ed. New York, Macmillan Publishing Co, 1975, pp 174-179
3. Noble J, Matthew H: Acute poisoning by TCA's: Clinical features and management of 100 patients. Clin Tox 2:403, 1969
4. Thorstrand C: Cardiovascular effects of poisoning with TCA's. Acta Med Scand 195:505-514, 1974
5. Manoguerra AS: Poisoning with tricyclic antidepressant drugs. Clin Tox 10:149-158, 1977
6. Wood CA, Brown JR, Coleman JH, et al: Management of tricyclic antidepressant toxicities. Dis Nervous System 37:459-461, Jul/Dec 1976
7. Fowler NO, McCall D, Te-Chuan C, et al: Electrocardiographic changes and cardiac arrhythmias in patients receiving psychotropic drugs. Am J Cardiol 37:223-230, Feb 1976
8. Robinson DS, Barker E: Tricyclic antidepressant cardiotoxicity. JAMA 236:2089-2090, Nov 1, 1976
9. Vohra J, Burrows G, Hunt D, et al: The effect of toxic and therapeutic doses of tricyclic antidepressant drugs on intracardiac conduction. Europ J Cardiol 3:219-227, 1975
10. Kristiansen ES: Cardiac complications during treatment with imipramine (Tofranil). Acta Psychiat Neurol Scand 36:427-442, 1961
11. Moir DC: Tricyclic antidepressants and cardiac disease. Am Heart J 86:841-842, Dec 1973
12. Vohra J, Burrows GD, Sloman G: Assessment of cardiovascular side effects of therapeutic doses of tricyclic antidepressant drugs. Aust N Z J 5:7-11, 1975
13. Coull DC, Dingwall-Fordyce I, Crooks J, et al: Amitriptyline and cardiac disease—Risk of sudden death identified by monitoring system. Lancet 2:590-591, Sep 19, 1970
14. Kantor SJ, Bigger JT, Glassman AH, et al: Imipramine-induced heart block—A longitudinal case study. JAMA 231: 1364-1366, Mar 31, 1975
15. Nymark M, Rasmussen J: Effect of certain drugs upon amitriptyline induced electrocardiographic changes. Acta Pharmacol Toxicol 24:148-156, 1966
16. Dumovic P, Burrows GD, Vohra J, et al: The effect of tricyclic antidepressant drugs on the heart. Arch Toxicol 35:255-262, 1976
17. Vohra J, Hunt D, Burrows G, et al: Intracardiac conduction defects following overdose of tricyclic antidepressant drugs. Europ J Cardiol 2:453-458, 1975
18. Moir DC, Cornwell WB, Dingwall-Fordyce I, et al: Cardiotoxicity of amitriptyline. Lancet 2:561-564, Sep 16, 1972
19. Thorstrand C: Cardiovascular effects of poisoning with tricyclic antidepressants. Acta Med Scand 195:505-514, 1974
20. Sigg EB, Osborn M, Korol B: Cardiovascular effects of imipramine. J Pharmacol Exp Ther 141:237-243, Aug 1963
21. Cocco G, Ague C: Interactions between cardioactive drugs and antidepressants. Europ J Clin Pharmacol 11:389-393, 1977
22. Surawicz B, Lasseter KC: Effect of drugs on the electrocardiogram. Prog in Cardiovasc Dis 8:26-55, Jul 1970
23. Jandhyala BS, Steenberg ML, Perel JM ,et al: Effects of several tricyclic antidepressants on the hemodynamics and myocardial contractility of the anesthesized dogs. Europ J Pharmacol 42:403-410, 1977
24. Fouron JC, Chicoine R: ECG changes in fatal imipramine (Tofranil) intoxication. Pediatrics 48:777-781, Nov 1971
25. Freeman JW, Mundy GR, Beattie RR, et al: Cardiac abnormalities in poisoning with tricyclic antidepressants. Br Med J 2:610-611, 1969
26. Brackenridge RG, Peters TJ, Watson JM: Myocardial damage in amitriptyline and mortriptyline poisoning. Scot Med J 13:208, 1968
27. Roberts RJ, Mueller S, Lauer RM: Propranolol in the treatment of cardiac arrhythmias associated with amitriptyline intoxication. J Pedr 82:65-67, 1973
28. Heiman EM: Cardiac toxicity and thioridazine tricyclic antidepressant combination. J Nerv Dis 165:139-143, 1977
29. Brown TCK: Sodium bicarbonate treatment for tricyclic antidepressant arrhythmias in children. Med J Aust 2:380-383, 1976
30. Brown TCK: Tricyclic antidepressant overdosage: Experimental studies on the management of circulatory complications. Clin Tox 9:255-272, 1976
31. Brown TCK, Barker GA, Dunlop ME, et al: The use of sodium bicarbonate in the treatment of TCA-induced arrhythmias: Anaesth Intens Care 1:203-210, 1976
32. Slovis TL, Ott JE, Teitelbaum DT, et al: Physostigmine therapy of acute tricyclic antidepressant poisoning. Clin Tox 4: 451-459, Sep 1971
33. Bismuth C, Pebay-Peyroula F, Frejaville J: Present day therapy of toxic cardiomyopathies. Concours Med 91(Suppl 21): 4453-4470, 1969
34. $NaHCO_3$ and TCA poisoning (Editorial). Lancet 2:838, Oct 1976
35. Moir DC, Cornwell WB, Dingwall-Frodyce I, et al: Cardiotoxicity of amitriptyline. Lancet 2:561-564, Sep 16, 1972
36. Biggs JT, Spiker DG, Petit JM: Tricyclic antidepressant overdose. JAMA 238:135-138, Jul 11, 1977
37. Petit JM, Spiker DG, Ruwitch JF, et al: Tricyclic antidepressant plasma levels in adverse effects after overdose. Clin Pharmacol and Ther 21:47-51, 1977
38. Glassman AH, Jurwic MJ, Perel JM: Plasma binding of imipramine and clinical outcome. Am J Psych 130:1367-1369, Dec 1973
39. Physostigmine: Rational use (Editorial). JACEP 5:541, Jul 1976
40. Sedal L, Korman MG, William PO, et al: Overdosage of tricyclic antidepressants: A report of two deaths and a prospective study of 24 patients. Med J Aust 2:74-79, 1972
41. Spiker DG, Biggs JT: Tricyclic antidepressants: Prolonged plasma levels after overdose. JAMA 236:1711-1712, Oct 11, 1976
42. Masters AB: Delayed death in imipramine poisoning. Br Med J 3:866-867, Sep 30, 1967
43. Noble J: Acute poisoning by TCA's. Clin Tox 4:451, 1971
44. George AJ: The effects of three tricyclic antidepressants on arterial ^{3}HNA uptake and arterial responsiveness to noradrenaline (NA). Br J Pharmacol 57:432-433, 1976
45. Filczewski M, Szymanska-Kosmala M, Oledzka K: Biosynthesis of catecholamines, uptake of ^{3}H-noradrenaline, and reactivity of cardiovascular system of the rat after chronic and acute treatment with a new antidepressant agent, IPF C-45. Pol J Pharmacol 29:23-29, 1977
46. Kabes J, Poschlova N, Krsiak TD, et al: Tricyclic antidepressants and depletion of brain catecholamines: Preclinical and clinical studies with L-dopa. Activitas Nervosa Superior 18: 242, 1976
47. Nakamura M, Fukushima H: The effect of tricyclic antidepressants and neuroleptics on the peripheral and central action of norepinephrine in reserpine-treated mice. Europ J Pharmacol 38:342-348, 1976
48. Axelrod J, Whitby LG, Hertting G: Effect of psychotropic drugs on the uptake of ^{3}H-norephinephrine by tissues. Science 133:383-384, Feb 1961
49. Axelrod J, Hertting G, Potter L: Effect of drugs on the uptake and release of ^{3}H-norepinephrine in the rat heart. Nature 194:297, Apr 21, 1962
50. Franco R, Bonaccorsi A, Castelli MG, et al: Relationships between chronotropic effect, 1-^{3}H-noradrenaline uptake and tissue concentrations of desirpramine, protriptyline and doxepin in rat isolated atria. Arch Int Pharmacodyn 224:55-65, 1976
51. Boakes AJ, Laurence DR, Teoh PC, et al: Interactions between sympathomimetic amines and antidepressant agents in man. Br Med J 1:311-315, 1973
52. Borga O, Hamberger B, Malmfors T, et al: The role of plasma protein binding in the inhibitory effect of nortriptyline on the neuronal uptake of norepinephrine. Clin Pharmacol Ther 11:581-588, 1970
53. Borga O, Azarnoff DL, Forshell GP, et al: Plasma protein binding of tricyclic antidepressants in man. Biochem Pharmacol 18:2135-2138, 1969
54. Glassman AH, Hurwic MJ, Perel JM: Plasma binding of imipramine and clinical outcome. Am J Psych 130:1367-1369, Dec 1973
55. Bigger JT Jr, Giardina EGV, Perel JM, et al: Cardiac antiarrhythmic effect of imipramine hydrochloride. N Engl J Med 296:206, 1977
56. Kantor SJ, Glassman AH, Bigger JT Jr, et al: The cardiac effects of therapeutic plasma concentrations of imipramine. Am J Psychiatry 135:534, 1978
57. Vohra J, Burrows G, Hunt D, et al: The effect of toxic and therapeutic doses of tricyclic antidepressant drugs on intracardiac conduction. Eur J Cardiol 3:219, 1975
58. Kerr F, Kenoyer G, Bilitch M: Quinidine overdose—Neurologic and cardiovascular toxicity in a normal person. Br Heart J 33:629, 1971
59. Hoffman BF, Rosen MR, Wit AL: Electrophysiology and pharmacology of cardiac arrythmias—VII. Cardiac effects of quinidine and procaine amide. B Am Heart J 90:117, 1975
60. Shub C, Gau GT, Sidell PM, et al: The management of acute quinidine intoxication. Chest 73:173, 1978
61. Sizyer RB, Clark JK, Barker ES, et al: The acute effects in man of rapid intravenous infusion of hypertonic sodium bicarbonate solution. Medicine 34:51, 1955
62. Conn HL, Luchi RJ: Some quantitative aspects of the binding of quinidine and related quinoline compounds by human serum albumin. J Clin Invest 40:509, 1961
63. Gerhardt RE, Knouss RF, Thyrum PT, et al: Quinidine excretion in aciduria and alkaluria. Ann Intern Med 71:927-933, Nov 1969
64. Burks JS, Walker JE, Rumack BH, et al: Tricyclic antidepressant poisoning: Reversal of coma, choreoathetosis, and myoclonus by physostigmine. JAMA 230:1405-1407, Dec 4, 1974
65. Snyder BD, Blonde L, McWhirter WR: Reversal of amitryptiline intoxication by physostigmine. JAMA 230:1433-1434, Dec 4, 1974
66. Newton RW: Physostigmine salicylate in the treatment of tricyclic antidepressant overdosage. JAMA 231:942-943, Mar 3, 1975
67. Katz RL, Katz GJ: Clinical experience with parasympathomimetics and anticholinesterases in anesthesia, *In* Nahas GC, Salamagne JC, Vears P, et al (Eds): Le Systeme Cholinergique. Paris, Librarie Arnette, 1972
68. Chin LS, Havill JH, Rothwell RP, et al: Use of physostigmine in tricyclic antidepressant poisoning. Anesth Intensive Care 4:138-140, May 1976
69. Langslet A, Johansen WG, Ryg M, et al: Effects of dibenzepine and imipramine on the isolated rat heart. Europ J Pharmacol 14:333-339, May 1971

Refer to: Peters KS, Tong TG, Kutz K, et al: Diabetes mellitus and orthostatic hypotension resulting from ingestion of Vacor rat poison: Endocrine and autonomic function studies. West J Med 134:65-68, Jan 1981

Diabetes Mellitus and Orthostatic Hypotension Resulting From Ingestion of Vacor Rat Poison: Endocrine and Autonomic Function Studies

KENNETH S. PETERS, MD
THEODORE G. TONG, PharmD
KATHLEEN KUTZ, PharmD
NEAL L. BENOWITZ, MD
San Francisco

VACOR RAT POISON, which contains n-3-pyridylmethyl-n'-P-nitrophenyl-urea (PNU), was marketed in the United States beginning in 1975. After numerous cases of poisoning by this product, some lethal and many resulting in apparently irreversible diabetes mellitus and autonomic and peripheral neuropathies,[1-5] Vacor was removed from the market in 1979. However, this poison is still on some store shelves and in private homes, and cases of human poisoning continue to be reported. We describe the case of a young man who ingested Vacor. Our patient's condition has been observed for over a year and specific studies of endocrine and autonomic nervous functions have been carried out.

Report of a Case

A 24-year-old man was admitted to the San Francisco Veterans Administration Hospital in August 1977 because of nausea and vomiting, abdominal pain, diffuse muscle pain, and increased frequency of urination and thirst. He had been in good health until a week before admission when he ingested one packet (39 grams containing 2 percent PNU) of Vacor rat poison in a suicide attempt. The patient had no history of diabetes or previous polyuria, polydipsia or polyphagia. Physical examination at the time of discharge from the Navy three weeks earlier showed no abnormalities.

On admission the patient was lethargic and in moderate distress. Blood pressure was 120/80 and 100/70 mm of mercury and heart rate 88 and 100 beats per minute while in the recumbent and sitting positions, respectively. Bowel sounds were decreased; there was diffuse epigastric tenderness but no rebound, guarding or masses. Chest, cardiac and neurological examinations showed no abnormalities.

Results of laboratory tests included the following: arterial blood gas measurements were oxygen pressure (Po_2) 108 mm of mercury and carbon dioxide (Pco_2) 26.7 mm of mercury; pH was 7.20; blood glucose was 1,280, urea nitrogen 157 and creatinine 3.0 mg per dl; serum sodium was 131, potassium 5.4, chloride 84 and bicarbonate 10.6 mEq per liter. Serum ketones were 1+; analysis of urine showed that the reaction for glucose was 3+ and for ketones was 4+. Electrocardiogram showed normal sinus rhythm with peaked T waves in leads V_2 to V_6.

Treatment with intravenously given fluids, potassium and continuous low-dose infusion of insulin was started; hyperglycemia, ketosis, glycosuria and ketonuria responded promptly to treatment. The patient did not report that he had ingested Vacor until the second hospital day. Therefore, at this time intravenous infusion of 500 mg of nicotinamide every six hours was begun and continued from days three to seven. Approximately a week after admission the patient began to complain of symptoms of orthostatic lightheadedness and subsequently experienced one episode of orthostatic syncope. Orthostatic hypotension was noted: blood pressure was 120/90 mm of mercury during recumbency and 80/60 mm of mercury on standing. The use of elastic stockings and oral administration of 0.3 mg of fludrocortisone per day seemed to improve the degree of hypotension sufficiently to enable ambulation. The diabetes was subsequently controlled with 40 units of NPH (neutral protamine-Hage-

From the Clinical Pharmacology Unit of the Medical Service, San Francisco General Hospital Medical Center, and the Departments of Medicine and Clinical Pharmacy, University of California, San Francisco.

Submitted, revised, April 8, 1980.

Supported in part by Grants DA01696, AM06405 and HE11046 from the National Institutes of Health. The studies were carried out in the General Clinical Research Center RR-00083.

Reprint requests to: Neal L. Benowitz, MD, Clinical Pharmacology Unit 5H4, San Francisco General Hospital, 1001 Potrero Avenue, San Francisco, CA 94110.

dorn) insulin administered subcutaneously each morning. Blood glucose concentrations ranged between 250 and 300 mg per dl throughout the day. Over the subsequent months the patient was readmitted to hospital several times for both hypoglycemia and ketoacidosis. In May 1978, approximately ten months after Vacor ingestion, the patient was admitted to San Francisco General Hospital Medical Center because of ketoacidosis. He responded to usual treatment and after recovery was transferred to the Clinical Study Center for better characterization of his endocrine and autonomic nervous functions. Studies were carried out while the patient was treated with 0.3 mg per day of orally given fludrocortisone and then again three weeks after cessation of this medication.

Methods*

The patient was placed on a 2,400 calorie (40 percent carbohydrate, 43 percent fat, 17 percent protein) diet supplemented with 100 mEq of sodium per day. All urine was collected for determination of electrolyte, catecholamine[6] and aldosterone[7] excretion. Plasma renin activity[8] was measured after overnight recumbency and after four hours of upright posture. Plasma and erythrocyte volumes were determined by distribution of albumin labeled with radioactive iodine.

Supine blood pressure and heart rate responses to upright posture were measured each morning before breakfast. Blood pressure was measured using an infrasonic pressure transducer (Infrasonde, Sphygmetrics, Inc., Woodland Hills, CA) placed over the brachial artery; heart rate was monitored continuously by a Grass Model D5 polygraph. The plasma norepinephrine concentrations were measured[9] in venous blood samples collected while the patient was supine, 30 minutes after insertion of an indwelling butterfly catheter, and again after standing for 10 minutes. Infusion of tyramine and norepinephrine was done to assess adrenergic stores and vascular sensitivity to norepinephrine, respectively. Insulin C-peptide was measured in plasma by radioimmunoassay (Calbiochem-Behring Corp., San Diego, CA, reagent system). Capillary basement membrane thickness was measured on quadriceps muscle biopsy specimens according to the method of Siperstein and co-workers.[10]

*Dr. Morris Schambelan carried out measurements of urinary aldosterone concentrations and plasma renin activity, Dr. Michael Roizen measured plasma catecholamines, Dr. Marvin Siperstein measured muscle capillary basement membrane thickness and Dr. John Karam assessed serum C-peptide.

Results

Biochemical and physiological data obtained during and after discontinuation of fludrocortisone therapy are given in Table 1. Average urinary sodium and potassium excretion rates were similar in the two study periods. The 24-hour urinary excretion rates for norepinephrine and epinephrine were within normal limits, whereas 24-hour urinary excretion of aldosterone was abnormally low, both before and after cessation of treatment with fludrocortisone. Plasma volume, based on idealized body weight, was within the normal range, whereas total blood volume and erythrocyte volume were slightly decreased; all were unaffected by cessation of fludrocortisone therapy. Plasma renin activity was at the lower limits of detection while the patient was supine and did not increase with upright posture during fludrocortisone therapy; however, supine renin activity and postural response became normal after discontinuation of fludrocortisone.

Blood pressure and heart rate responses to

TABLE 1.—*Biochemical and Physiological Data During and After Discontinuation of Fludrocortisone*

	Study Period 1 (FC)	*Study Period 2 (No FC)*	*Laboratory Normal Range*
Body weight (kg)	49.7	48.2	..
Urinary sodium (mEq/24 hr)	101.0	124.0	..
Urinary potassium (mEq/24 hr)	55.0	52.0	..
Urinary aldosterone (μg/24 hr)	2.4	2.7	4-19
Urinary norepinephrine (NE) (μg/24 hr)	42.0	..	10-70
Urinary epinephrine (μg/24 hr)	13.0	..	0-20
Blood volume (ml/kg)	59.2	60.2	60-76
Plasma volume (ml/kg)	39.1	40.3	36-44
Erythrocyte volume (ml/kg)	20.0	20.0	24-32
Supine PRA	<0.1	2.6	0.7-2.6
2 hr upright PRA	<0.1	6.4	1.1-7.9
Supine plasma norepinephrine (pg/ml)	..	264.0	..
10 minutes standing NE (pg/ml)	..	628.0	..
ΔBP—infusion tyramine (20 μg/kg/min)	42/18	32/22	..
ΔBP—infusion NE (5 μg/min)	44/28	40/34	..

BP = blood pressure; FC = fludrocortisone; PRA = plasma renin activity

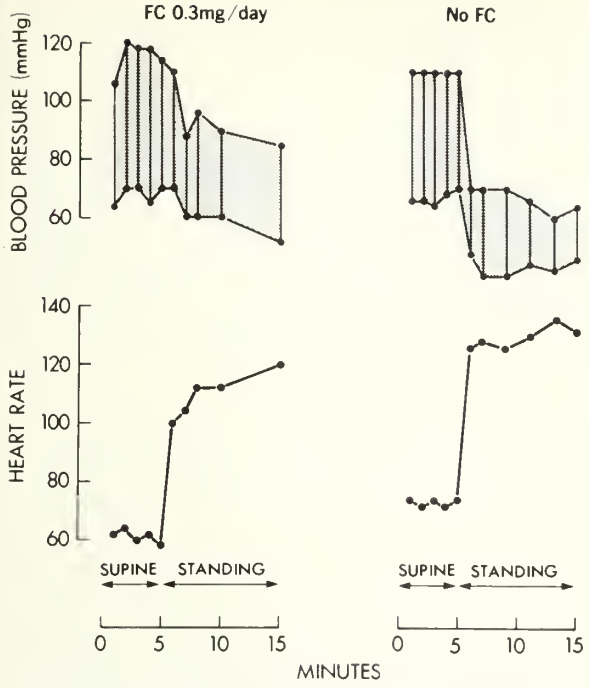


Figure 1.—Orthostatic blood pressure and heart rate responses during and after fludrocortisone (FC) treatment. Measurements of standing blood pressure were higher and heart rate lower during FC treatment.

standing for ten minutes before and after fludrocortisone therapy are shown in Figure 1. Recumbent plasma norepinephrine concentrations and response to standing, measured only after discontinuation of fludrocortisone, were within the normal range.[11] Pressor responses to tyramine and norepinephrine were greater than those reported in the literature[12-14] and were similar during the two study periods. Insulin C-peptides were undetectable in plasma, suggesting no endogenous production of insulin. Capillary basement membrane thickness measured in August 1977, four weeks after ingestion of Vacor, was 1,642 Å±93 (SD). A repeat biopsy done in October 1978 showed no significant change in capillary basement membrane thickness, 1,738 Å±191. Nerve conduction velocity of the right peroneal nerve (40 msec) and the left ulnar (75 msec with distal latency, 2 msec) were within normal limits.

Discussion

The syndrome of new-onset diabetes mellitus with severe orthostatic hypotension typically follows Vacor ingestion.[1-5] Other reported manifestations of the autonomic neuropathy include dysphagia, constipation or diarrhea, impotence, and bladder dystonia and dysfunction. None of these was present in our patient. In another case of Vacor ingestion, there was evidence of sensory and motor peripheral neuropathy with weakness of the lower extremities and ataxia.[3] Our patient had normal peripheral sensory and motor functions.

To understand the natural history of the Vacor syndrome better, we reevaluated our patient's condition approximately a year after ingestion of the rat poison. Based on the findings of absence of insulin C-peptide in plasma[15] and the clinical features of brittle diabetes, it appears that Vacor completely destroyed pancreatic β-islet tissue. Skeletal muscle capillary basement membranes were of normal thickness when measured four weeks after Vacor ingestion and were relatively unchanged 14 months later. Capillary basement membrane thickness has been interpreted as an indicator of diabetic microangiopathy.[10,16] The finding of normal thickness suggests that microangiopathy was not present at the time of Vacor ingestion and is consistent with the toxic rather than genetic basis for our patient's diabetes. Normal findings of a follow-up biopsy done 14 months later suggests that little microangiopathy had developed yet, despite poor control of blood glucose. Longer follow-up is necessary to ascertain if the natural history of Vacor-induced diabetes is similar to that of genetic diabetes.

Orthostatic hypotension persisted during the year of follow-up in our patient. However, the patient had adapted so that he rarely experienced orthostatic dizziness, despite the pronounced fall in blood pressure. Evaluation of adrenergic function showed normal 24-hour urinary catecholamine excretion and normal plasma norepinephrine concentrations in supine and upright positions. The pressor response to tyramine confirmed that neuronal catecholamine stores were normal. The normal plasma norepinephrine response to upright posture and the increased pressor sensitivity to infused norepinephrine indicated that adrenergic efferent neural pathways and arteriolar receptor sensitivity were intact. However, the observed pressor hypersensitivity to norepinephrine is consistent with denervation hypersensitivity and suggests a partial preganglionic adrenergic efferent lesion. Tachycardia with upright posture indicated that baroreceptor afferent and cardiac efferent pathways and cardiac chronotropic receptors functioned normally.

It is possible that Vacor specifically affected

the venous circulation such that venomotor tone was not maintained with upright posture, resulting in venous pooling and hypotension. Deficient reflex venoconstriction with normal arterial vasoconstriction, which has been reported in a few patients with Shy-Drager syndrome and idiopathic orthostatic hypotension,[17] might explain postural hypotension despite apparently normal overall adrenergic function. Hypovolemia may have also contributed to postural hypotension. Our patient did have a borderline low blood volume that persisted despite fludrocortisone and salt treatment. Inability to retain sodium despite mineralocorticoid therapy has been documented in persons with drug-induced adrenergic neuronal blockade.[18] In another patient who ingested Vacor, disabling orthostatic hypotension and total functional destruction of vascular adrenergic nerves have been described.[19] Our patient, whose adrenergic function was reasonably well preserved and who had no other manifestations of autonomic neuropathy, presumably experienced the less severe effects of Vacor neurotoxicity.

Fludrocortisone therapy had no effect on blood or plasma volume and had a modest effect on the extent of orthostatic hypotension. During fludrocortisone therapy, plasma renin activity and urinary aldosterone excretion were abnormally low. Plasma renin activity returned to normal levels, but urinary aldosterone excretion remained low three weeks after discontinuation of fludrocortisone. The latter suggests that Vacor may have adrenocortical toxic effects that have not been reported previously. Although we cannot exclude the possibility that higher doses of fludrocortisone might have been more beneficial to our patient, poor clinical response to fludrocortisone has been reported in another patient with orthostatic hypotension resulting from Vacor ingestion.[2]

Pretreatment of rats with nicotinamide can prevent or ameliorate PNU toxicity.[20] Similarly, nicotinamide can protect against the diabetogenic effects of streptozocin and the diabetogenic and neurotoxic effects of 6-aminonicotinamide.[21,22] All three of the toxins have structural similarities and are suspected to antagonize the actions of nicotinamide. On this basis, nicotinamide has been advocated as treatment for PNU ingestion in humans.[23] Our patient first received nicotinamide nine days after ingesting PNU and no beneficial effect was apparent. However, if the results of animal studies are applicable to humans, the larger the dose and the earlier the treatment with nicotinamide, the greater should be the benefit. Unfortunately, the appearance of toxicity and the diagnosis of Vacor poisoning are often delayed, so that nicotinamide is administered late in the clinical course at which time it may be ineffective. The maximum dosage of nicotinamide that can be tolerated in humans is unknown, but several patients have received from 2 to 3 grams over 24 hours, administered intravenously in four divided doses, without apparent side effects.[24]

REFERENCES

1. Lee TH, Kim YS, Chung MY, et al: Clinical prospective study of rodenticide RH-787 intoxication in humans. Korean J Int Med 20:530-537, 1977

2. Prosser PR, Karam JH: Diabetes mellitus following rodenticide ingestion in man. JAMA 239:1148-1150, 1978

3. Miller JV, Stokes JD, Silpipat C: Diabetes mellitus and autonomic dysfunction after vacor rodenticide ingestion. Diabetes Care 1:73-76, 1978

4. Pont A, Rubino JM, Bishop D, et al: Diabetes mellitus and neuropathy following vacor ingestion in man. Arch Intern Med 139:185-187, 1979

5. LeWitt PA: Neurotoxicity of the rat poison, Vacor. N Engl J Med 302:73-77, 1980

6. Euler US von, Floding I: A fluorimetric micromethod for differential estimation of adrenaline and noradrenaline. Acta Physiol Scand 33 (Suppl 118):45-56, 1955

7. New MI, Miller B, Peterson RE: Aldosterone excretion in normal children and in children with adrenal hyperplasia. J Clin Invest 45:412, 1966

8. Stockigt JR, Collins RD, Noakes CA, et al: Renal-vein renin in various forms of renal hypertension. Lancet 1:1194-1198, 1972

9. Roizen MF, Moss J, Henry DP, et al: Effects of halothane on plasma catecholamines. Anesthesiology 41:432-439, 1974

10. Siperstein MD, Unger RH, Madison LI: Studies of muscle capillary basement membranes in normal subjects, diabetic and pre-diabetic patients. J Clin Invest 47:1973-1999, 1968

11. Kopin IJ, Lake RC, Ziegler M: Plasma levels of norepinephrine. Ann Intern Med 88:671-680, 1978

12. Cohn JN: Comparative cardiovascular effects of tyramine, ephedrine, and norepinephrine in man. Circul Res 16:174-182, 1965

13. Demanet JC: Usefulness of noradrenaline and tyramine infusion tests in the diagnosis of orthostatic hypotension. Cardiology 61 (Suppl 1):213-224, 1976

14. Rogers WK, Benowitz NL, Wilson KM, et al: Effect of disulfiram on adrenergic function. Clin Pharmacol Ther 25:469-477, 1979

15. Horwitz DL, Kuzuya H, Rubenstein AH: Circulating serum C-peptide—A brief review of diagnostic implications. N Engl J Med 295:207-209, 1976

16. Diabetic microangiopathy—Medical Staff Conference, University of California, San Francisco. West J Med 121:404-412, Nov 1974

17. Kontos HA, Richardson DW, Norvell JE: Mechanisms of circulatory dysfunction in orthostatic hypotension. Trans Am Clin Climatol Assoc 87:26, 1976

18. Gill JR, Mason DT, Bartter FC, et al: Adrenergic nervous system in sodium metabolism: Effects of guanethidine and sodium-retaining steroids in normal man. J Clin Invest 43:177-184, 1964

19. Benowitz NL, Byrd R, Schambelan M, et al: Dihydroergotamine treatment for orthostatic hypotension from vacor rodenticide. Ann Intern Med 92:387-388, 1980

20. Lazarus SS, Shapiro SH: Influence of nicotinamide and pyridine nucleotides on streptozotocin and alloxan-induced pancreatic B cell cytotoxicity. Diabetes 22:499-506, 1973

21. Herken H, Lange K, Kolbe H, et al: Antimetabolic action on the pentose phosphate pathway in the central nervous system induced by 6-aminonicotinamide. *In* Genazzani E, Herken H (Eds): Central Nervous System: Studies in Metabolic Regulation and Function. Berlin, Springer-Verlag, 1974, pp 41-54

22. Herken H: Antimetabolic action of 6-aminonicotinamide on the pentose phosphate pathway in the brain. *In* Aldridge WN (Ed): Mechanisms of Toxicity, London, Macmillan, 1971, pp 189-203

23. Vacor Ratkiller (revised). HEWS-DUS-FDA 116th Supplement. National Clearinghouse for Poison Control Center, Apr 1977

24. Winter SL, Boyer JL: Hepatic toxicity from large doses of vitamin B_3 (nicotinamide). N Engl J Med 289:1180-1182, 1973

Refer to: Moses FM, Buscemi JH: Obstructive sleep apnea syndrome associated with nasopharyngeal carcinoma. West J Med 134:69-70, Jan 1981

Obstructive Sleep Apnea Syndrome Associated With Nasopharyngeal Carcinoma

CAPT FRANK M. MOSES, MC, USA
Washington, DC

LT COL JON H. BUSCEMI, MC, USA
Aurora, Colorado

THE SLEEP APNEA SYNDROME consists of at least 30 apneic episodes observed in both rapid eye movement (REM) and non-REM sleep, some of which must appear in a repetitive sequence in non-REM sleep. It is a well-described symptom complex manifested by excessive daytime hypersomnolence, hypnagogic hallucinations, personality and sexual behavior changes and hypertension.[1,2] The syndrome has been subdivided into central, upper airway obstructive and mixed apnea according to pathogenic mechanisms. Rare cases of upper airway obstructive apnea have documented structural abnormalities.[2-9] We present the case of a patient referred for evaluation of a sleep disorder with associated severe hypertension. The patient's condition was diagnosed as the sleep apnea syndrome, upper airway obstructive type, secondary to a poorly differentiated epidermoid carcinoma of the nasopharynx.

Report of a Case

A 43-year-old black man was admitted to hospital with hypertension and frequent inappropriate episodes of falling asleep. Eighteen months before admission, hypertension had been noted and was treated medically for six months. Six months before admission, otitis media had been treated with a myringotomy tube in an ear, nose and throat clinic. Three months later disabling daytime hypersomnolence and episodes of hypnagogic hallucinations were noted. A month before admission dextroamphetamine sulfate therapy was begun for presumed narcolepsy. The patient was admitted to another hospital with a blood pressure of 180/140 mm of mercury, mild azotemia, mental confusion and grade 4 hypertensive retinopathy. He was treated vigorously for hypertension and transferred to Fitzsimons Army Medical Center.

On physical examination the patient was a well-developed, normocephalic, slightly obese man who snored loudly and was easily aroused from sleep. The patient was 183 cm (6 feet) tall, 95 kg (209 pounds), normotensive and afebrile. He was found to have grade 4 hypertensive retinopathy, a myringotomy tube on the left side, slightly edematous nasal mucosa and normal oropharynx. Laboratory findings gave the following values: blood urea nitrogen (BUN) 25 mg per dl, creatinine 1.5 mg per dl and lactate dehydrogenase (LD) 389 units per ml. Analysis of urine showed granular and hyaline casts and proteinuria. The remainder of the physical examination and standard laboratory tests gave normal results. The sleep apnea syndrome was suspected by history and clinically verified by sleep observation during which multiple episodes of apnea, despite continued thoracic respiratory effort, were noted. An electroencephalogram showed abnormal development of REM for light sleep with apneic episodes observed. Study of pulmonary function flow-volume loops was consistent with extrathoracic obstruction. Findings on a brain scan were normal. Sleep monitoring failed to disclose significant arrhythmias or oxygen desaturation. Nasopharyngeal and retropharyngeal swelling with airway compromise was observed on a xerogram. Examination under general anesthesia detected a lymphoid mass in the nasopharynx, which completely obstructed the right choana, 50 percent of the left choana and both eustachian tubes. Pathological diagnosis was benign lymphoid hyperplasia and a tracheostomy was done. Hypertension and daytime hypersomnolence resolved within four days without administration of any medications.

In two weeks the tracheostomy was closed and, despite a lack of change in mass size as indicated by xerography, the patient did well and the case was followed on an outpatient basis for six weeks. However, the patient then returned with recurrent

From the Department of Medicine (FMM), and Neurology Service, Department of Medicine (JHB), Fitzsimons Army Medical Center, Aurora, Colorado. Dr. Moses is now affiliated with Walter Reed Army Medical Center, Washington, DC.

Submitted, revised, May 21, 1980.

The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or Department of Defense.

Reprint requests to: Capt Frank M. Moses, MC, USA, Gastroenterology Service, Dept. of Medicine, Walter Reed Army Medical Center, Washington, DC, 20012.

symptoms of hypersomnolence, excessive snoring, cervical lymphadenopathy, a weight gain of 6 kg and hypertension of 180/120 mm of mercury. He was treated medically for his hypertension and a repeat tracheostomy was carried out. A submandibular lymph node biopsy was done and the specimen disclosed poorly differentiated epidermoid carcinoma. Repeat panendoscopy with biopsy of an exophytic posterior nasopharyngeal mass confirmed the diagnosis.

All symptoms referable to sleep apnea syndrome, including hypertension, cleared again within three to five days after the tracheostomy. Administration of antihypertensive medications was discontinued and the patient remained normotensive. The patient was treated with local radiation therapy and remained without evidence of recurrent sleep apnea syndrome until his death three months later. Pulmonary, hepatic, splenic and osteoid metastatic lesions developed and the patient was treated unsuccessfully with systemic chemotherapy before his death.

Discussion

The sleep apnea syndrome is found in patients with the Shy-Drager syndrome, myotonic dystrophy, narcolepsy and hypothyroidism.[10] It has also been reported to be familial.[11] Most cases of sleep apnea syndrome are secondary to upper airway obstruction and usually are caused by intermittent hypotonia of the soft palate and tongue musculature.[1-6] Rare cases of obstructive sleep apnea syndrome result from anatomic abnormalities such as enlarged tonsillar and adenoidal tissue, lymphoma, acquired micrognathia, micrognathia associated with the Scheie syndrome, nasal deformities and laryngeal webs.[7-9]

To the authors' knowledge this is the first report of a case of obstructive sleep apnea syndrome secondary to nasopharyngeal carcinoma. The case illustrates many features of this syndrome and the variety of problems that may occur before determining the correct diagnosis and therapy. Hypertension was noted in 56 percent of patients in one study of obstructive sleep apnea and was usually moderate.[2] In our patient, however, hypertension was a prominent feature that responded to appropriate therapy for the underlying sleep apnea syndrome. The syndrome is becoming increasingly recognized as a relatively common sleep disorder and should be suspected in the clinical setting as outlined by others.[1,2] The involvement of organs adjacent to the nasopharynx should heighten suspicion of structural abnormalities and appropriate evaluation should be made.[12,13]

Summary

A patient was referred for evaluation of excessive hypertension and a sleep disorder. This condition was diagnosed as sleep apnea syndrome secondary to upper airway obstruction caused by a poorly differentiated epidermoid carcinoma of the nasopharynx. Sleep apnea syndrome is becoming increasingly recognized as a relatively common sleep disorder. Involvement of organs adjacent to the nasopharynx should heighten suspicion of anatomic lesions obstructing airflow and necessitates appropriate evaluation.

REFERENCES

1. Guilleminault C, Tilkian A, Dement WC: The sleep apnea syndromes. Ann Rev Med 27:465-484, 1976

2. Guilleminault C, Eldridge F, Tilkian A, et al: Sleep apnea syndrome due to upper airway obstruction. Arch Intern Med 137: 296-300, 1977

3. Glenn W, Gee J, Cole D, et al: Combined central alveolar hypoventilation and upper airway obstruction. Am J Med 64:50-60, 1978

4. Sackner M, Landa J, Forrest T, et al: Periodic sleep apnea—Chronic sleep deprivation related to intermittent upper airway obstruction and central nervous system disturbance. Chest 67: 164-170, 1975

5. Whitcomb M, Altman M, Clark R, et al: Central and obstructive sleep apnea. Chest 73:857-860, 1978

6. Zwillich C: The clinical significance of snoring. Arch Intern Med 139:24, 1979

7. Perks WH, Cooper RA, Bradbury S, et al: Sleep apnea in Scheie's syndrome. Thorax 25:85-91, 1980

8. Weitzman E, Pollack C, Borowiecki B: Hypersomnia-sleep apnea due to micrognathia. Arch Neurol 35:392-395, 1978

9. Mangat D, Orr W, Smith R: Sleep apnea, hypersomnolence, and upper airway obstruction secondary to adeno-tonsillar enlargement. Arch Otolaryngol 103:383-386, 1977

10. Weitzman ED: The syndrome of hypersomnia and sleep-induced apnea. Chest 75:414-415, 1979

11. Strohl KP, Saunders NA, Feldman NT, et al: Obstructive sleep apnea in family members. N Engl J Med 299:969-973, 1978

12. Farmer W, Littner M, Gee J: Assessment of therapy of upper airway obstruction. Arch Intern Med 137:309-312, 1977

13. Simmons F, Guilleminault C, Dement W, et al: Surgical management of airway obstruction during sleep. Laryngoscope 87:338, 1977

Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

Pericardial Effusion in Association With Giant Cell Arteritis

To the Editor: The clinical spectrum of giant-cell arteritis has gradually emerged since the first report of temporal artery biopsy in this disease.[1] In the vast majority of cases the dominating symptoms and findings are referrable to arterial inflammation. However, nonspecific systemic features such as fever, anemia or abnormalities of liver function are being increasingly recognized as more bizarre presentations. We report here a case of giant cell arteritis associated with a pericardial effusion.

Report of a Case

A 69-year-old white woman was admitted to another hospital because of a one-month history of pronounced fatigue, malaise, fever and night sweats, as well as a weight loss of 5 to 6 pounds. Laboratory data showed a normochromic and normocytic anemia with a notably elevated erythrocyte sedimentation rate (125 mm per hour, Westergren). Leukocyte count and differential were normal. Results of thyroid function tests were normal. An x-ray study of the chest showed a right-sided aortic arch with mural calcification, but no other abnormalities. Other studies giving results within normal limits included an upper gastrointestinal study, barium enema, oral cholecystogram, excretory urogram, abdominal ultrasound, bone scan, bone marrow examination and a liver biopsy. Multiple blood cultures were negative. Empiric treatment for presumed subacute bacterial endocarditis was unsuccessful. Because of continuing symptoms over the next three weeks, the patient was referred to the University of Oregon Health Sciences Center for further evaluation.

There was no history of headaches, visual disturbances, arthralgias, myalgias or chest pain.

On admission she had an oral temperature of 37.7°C (100°F). Temporal arteries were not tender or thickened and had equal pulsations bilaterally. Funduscopic examination showed mild arteriolar narrowing and cotton wool spots on the right. She had a soft right carotid bruit. A grade I/VI systolic murmur was heard along the left sternal border without radiation. There were no gallops, extra heart sounds or friction rub. Findings on the rest of the physical examination were normal.

Routine laboratory data were unchanged. Serological tests for syphilis were negative. Serum protein electrophoresis and immunoelectrophoresis showed no monoclonal spike. Urine was negative for Bence-Jones protein. Analysis of urine gave normal findings and urine cultures were sterile. An electrocardiogram was within normal limits except for borderline low voltage in all leads. An echocardiogram showed a moderately large pericardial effusion. Six blood cultures, bone marrow cultures (bacterial, fungal and mycobacterial) and three urine cultures for mycobacteria were negative. Skin tests for tuberculosis (intermediate strength PPD), mumps, *Candida* organisms and trichophyton all failed to react. A liver-spleen scan was normal, as was computerized tomography of the patient's abdomen. Bilateral temporal artery biopsies were carried out. The right temporal artery was normal, but the left was grossly thickened and on microscopic section showed giant cell arteritis.

The patient was started on a regimen of 60 mg per day of prednisone. Dramatic improvement in symptoms and reduction of fever occurred within 24 hours. Five months after discharge all laboratory abnormalities had resolved (erythrocyte sedimentation rate, 20 mm per hour). She is at present doing well on a regimen of 7.5 mg per day of prednisone although a small pericardial effusion is still evident on echocardiography.

Comments

To the best of our knowledge pericardial effusion has never been described as a presumed manifestation of giant cell arteritis. An unrelated, coexistent cause for the effusion in our patient is always possible. However, consideration of the clinical symptoms, the results of the extensive investiga-

tions done and the patient's course following steroid therapy makes other explanations unlikely.

Pericardial involvement is well documented in other vasculitides such as periarteritis nodosa, hypersensitivity vasculitis and the vasculitis associated with rheumatoid arthritis and systemic lupus erythematosus. The present finding in giant cell arteritis is somewhat reminiscent of rheumatoid arthritis, where *silent* pericardial effusions are seen on echocardiography in about 50 percent of patients.[3] They are usually clinically benign, but can assume significance in the form of tamponade or constriction.[4] Although previously unreported, the frequency with which pericardial effusion may be encountered in giant cell arteritis is really unknown. An echocardiogram is not usually included or indicated in the workup of this disorder. Whether asymptomatic pericardial effusions are a common accompaniment of giant cell arteritis remains to be explored.

HARINDER S. GAREWAL, MD, PhD
RICHARD F. UHLMANN, MD
ROBERT M. BENNETT, MD
University of Oregon Health Sciences Center
Portland

REFERENCES

1. Horton BT, Magath TB, Brown GE: An undescribed form of arteritis of the temporal vessels. Mayo Clin Proc 7:700-701, 1932
2. Harrison MJG, Bevan AT: Early symptoms of temporal arteritis. Lancet 2:638-640, 1967
3. Franco AE, Levine HD, Hall AP: Rheumatoid pericarditis—Report of 17 cases diagnosed clinically. Ann Intern Med 77:837-844, 1972
4. John JT, Hough A, Sergent JS: Pericardial disease in rheumatoid arthritis. Am J Med 66:385-390, 1979

Magnesium—It's About Time

To the Editor: The article "Nutritional Aspects of Magnesium Metabolism" by Dr. Edmund B. Flink, which appeared in the October issue, was most timely, and covered some of the important aspects of magnesium in human health and disease. The accompanying editorial by Dr. Jerry K. Aikawa equally stressed the importance of this vital element, and also pointed out the neglect of this essential element by our profession. His opening statement summed it up quite well: "Among cations of biological importance, magnesium is the forgotten member."

Both writers failed to mention that there is a lot of interest in magnesium in some parts of the world. Since 1970 there have been two international conferences dealing with magnesium and its importance in health and disease, and the third international conference is being sponsored in part by the American College of Nutrition, and will take place in Baden-Baden, West Germany, in August 1981.

It is interesting, and somewhat sad, that in the pages between Flink's article and Aikawa's editorial was a Medical Staff Conference from the University of California, San Francisco, on sudden death, and nowhere during the conference was there any mention of magnesium. Even though Dr. Iseri at another campus of the same university has written extensively about the use of magnesium in ventricular tachycardias and fibrillations, none of the participants of the conference seemed to be aware of this. All kinds of drugs, enzymatic poisons and invasive techniques were suggested, and the concluding remark stated the following: "Better ways of evaluating the electrical stability of the ventricles and controlled trials of drug intervention are needed." But none suggested a trial of the safest of all methods and that with the fewest side effects—that is, magnesium therapy.

It is not that this is some newly discovered miracle cure. As long ago as July 1969 the *Annals of the New York Academy of Sciences* published a brilliant monograph by Raab entitled "Myocardial Electrolyte Derangement: Pluricausal, So-called Coronary Heart Disease (Dysionic Cardiopathy)," in which the author pointed out the value of magnesium and potassium in all kinds of cardiac disorders. A month later the same journal published another issue "The Pathogenesis and Clinical Significance of Magnesium Deficiency," which discussed the clinical significance of magnesium deficiency in all kinds of disorders, including tachyarrhythmias. Since that time, numerous articles have appeared in the world literature dealing with magnesium and its relationship to the heart, the kidneys, obstetrical and gynecological problems, pediatrics, neonatology, anesthesia and surgery and other fields. All had one thing in common—they were by and large totally ignored by our institutions of learning. Recently, Dr. Mildred Seelig of New York University published a new book *Magnesium Deficiency in the Pathogenesis of Disease—Early Roots of Cardiovascular, Skeletal, and Renal Abnormalities,* which should have been devoured by cardiologists and pediatricians, since it is divided about equally between pediatric and adult heart problems and their relationship to magnesium. I wonder how many of the cardiologists from the Medical Staff Conference are even aware of this book and, if they are, are interested in reading it.

The real tragedy is that sick people seem to get more information from the Rodale Press about their arrhythmias and heart disease than they get from their doctors and their medical schools. *Prevention,* the faddist magazine, has written extensively about the value of dolomite and other magnesium products such as chelated magnesium for heart disease, arrhythmias and hypertension. How much better is it to try a relatively safe nutritional supplement than to give poisons such as beta-blockers, digitalis or lidocaine, or to use invasive techniques with all their inherent complications and problems. Dr. Iseri has treated patients who have ventricular tachycardia and filbrillation with intravenously given magnesium; like others who have tried this method either primarily or at least when the conventional therapy did not work, he has observed some patients leave the hospital alive who otherwise would have died.

THE WESTERN JOURNAL OF MEDICINE has done a great service by calling this essential element to the attention of the medical community. It is hoped that finally some of the great institutions of learning take up this challenge, and begin to study this neglected element. It is certainly time.

BERNARD HORN, MD
El Cerrito, California

Mrs. Laennec and the Stethoscope

TO THE EDITOR: The day René Laennec invented the stethoscope way back in 1819 marked the beginning of today's highly sophisticated cardiology. We all know that. But here is a little known historical sidelight that led up to this important event.

It all started one evening when kindly old Dr. Laennec came home from a long day on the wards of Hospital Beaujou. Almost before he could slip off his frock coat, Mrs. Laennec waggled her finger at him, saying, "Now listen to me, René, this afternoon all the girls at the sewing circle were chattering about how you spend your day patting breasts and putting your ear to the bared bosoms of young maidens. I've never been so embarrassed in all my life!"

"My dear wife," responded the good doctor, "I'm only carrying on the scientific pursuit known as percussion and auscultation." "Pursuit is right," shrilled his spouse, "and you are going to have quit it. You are being too intimate, too personal with these patients!"

The poor doctor spent a troubled night, pitching and tossing, but toward the gray of the morning a brilliant thought struck him: If the deaf used a trumpet to amplify sound why couldn't he do the same in listening to heart sounds? First he constructed a cone-shaped trumpet of parchment. It worked. Next he carved out a wooden horn, tipped with ivory (to be warmer on the skin, of course) and that worked even better. René Théophile Laennec died just five years later, probably totally unaware of the significance of his discovery in the shaping of events that were to follow. He did publish, and leave for posterity, that classic work, "De l'auscultation mediate." History does not record who concluded that if listening with one ear is good, using both ears might double the effectiveness, and thereupon invented the binaural stethoscope. We do know, however, that early in this century, Joseph Bolivar De Lee, by simply taking advantage of the bone conduction of sound, introduced us to the head stethoscope, or fetus-scope. Now we could listen and record the augmented heart sounds of the intrauterine fetus.

Soon the stethoscope became the badge of practicing clinicians. We wore these precious personal tools about our necks on hospital rounds and in the office, and at all other times they were very visible in our suitcoat pockets. As interns and residents we prized and carefully guarded these instruments that enabled us to identify split second sounds and the diastolic murmurs of aortic insufficiency. We learned, too, that although Laennec had drawn the name of his invention from the Greek word for chest *(stethos),* this instrument had uses far beyond ausculation of the heart and lungs. When applied to the abdomen we could hear characteristic tinkles and peristaltic rushes; a bruit discovered in the flank, in the neck or in the extremities might lead us to a brilliant diagnosis. That was indeed the golden era of the stethoscope.

During the fateful 1960's we began to notice an ominous change. Now nurses were brazenly acquiring stethoscopes, and using them. Student nurses and emergency medical technicians had the audacity to drape them about their necks, instantly becoming junior doctors. Chiropractors and naturopaths were using them. And, alas, blood pressures were being taken in shopping malls and mail order companies advertised stethoscopes and sphygmomanometers for home use. A crowning insult was the use of this sacred instrument by auto mechanics to detect a *miss* in engine timing.

Physicians' patent right to the sole use of the stethoscope had obviously run out.

Fighting back we called technology to the breach. Let these other "health professionals" have the stethoscope. We would go one step further in scientific wizardry. We would develop telephonic transmission of electrocardiograms, with an instant computerized printout. We would introduce echocardiography by means of which we would not even have to see, touch or listen to a patient in order to make the most exotic diagnoses of cardiac function or dysfunction. We would hook new mothers and their babies up to monitors that would thump along, disgorging yards and yards of tape carrying information that could be transmitted directly to a consultant in a distant medical center who, in turn, could advise us when and whether operative interference was indicated.

Madame Laennec would be pleased to know that we are no longer guilty of being "too intimate, too personal." But her husband, the good Dr. Laennec, would undoubtedly shake his head in dismay and disbelief, certain that our skills in physical diagnosis were doomed to shrivel through atrophy and disuse.

E. R. W. FOX, MD
Special Editor for Idaho
Coeur d'Alene, Idaho

Protection Against Loss of Bone and Fracture in Postmenopausal Women

TO THE EDITOR: In the October issue of the journal E. E. Specht reviews the association between age-related bone loss and hip fracture in women and emphasizes the importance of prophylaxis, particularly estrogen, in the management of this common problem of the elderly.[1] Two points perhaps need additional emphasis.

The first is the association between bone mass and fragility. While a causal association is reasonable, and even probable, it is by no means certain. Many women without hip fracture have no more bone mass than those with fracture. No one knows why this is so. We can raise questions about bone quality, bone architecture and propensity to injury; but we cannot yet adequately evaluate these or other possible factors. Until we understand what makes those who fracture different from those who do not, we will not adequately understand the problem of osteoporosis.

This issue is not merely a matter of academic interest, for it is intimately linked to prophylaxis. Who should receive prophylaxis? Should it be those losing bone—that is, all postmenopausal women—or those most at risk for fracture?

Dr. Specht summarizes much of the evidence linking the male-female sex differential in bone loss to estrogen withdrawal at menopause and the corresponding evidence that estrogen therapy will abolish that sex differential. He also summarizes the belief of many that the risk of endometrial carcinoma has been overstated, particularly when compared with the counterposed risk of hip fracture.

Nevertheless, the question of routine postmenopausal estrogen therapy for the prevention of bone loss is a highly charged issue. I believe it unlikely that the Food and Drug Administration will approve long-term, routine use of estrogen for the prevention of age-related bone loss in *unselected* postmenopausal women, but will instead require limitation either to short treatment periods or to an identifiable, high-risk group. Because we do not know how to identify such a group today, a practicing physician is left in a quandary, from which he is not likely to be extricated soon.

This leads to the second point, namely, the role of calcium, both in bone loss and in its prophylaxis. Dr. Specht cites the only published, randomized, controlled studies of calcium prophylaxis,[2,3] and correctly points out that the degree of protection shown in these studies was intermediate between hormones and placebo. There he drops the matter.

Dr. Specht failed to cite our studies of calcium balance performance in perimenopausal women, in which we observed that the dietary requirement for calcium effectively increases at menopause to approximately 1.5 grams per day.[4] This change is produced by withdrawal of beneficial estrogenic effects on both calcium absorption efficiency and renal calcium conservation. These findings provide a theoretical base for the observed protection conferred by the calcium supplements in the studies cited by Dr. Specht.[2,3]

But protection against loss of bone and protection against fracture may be separate issues.

Items submitted for the Correspondence section should be typed double-spaced (including references) with conventional margins. The text should not exceed 600 words.

It is instructive, therefore, to call attention to a recent study by Matkovic and co-workers,[5] describing two ethnically and occupationally similar communities in Yugoslavia. One habitually received a high calcium intake, and the other low. Residents of the high-intake village had substantially greater bone mass and, more to the point, substantially fewer hip fractures, particularly among the elderly residents.

More such epidemiological work needs to be done; further, other questions need to be answered, such as required dose and bioavailability of various calcium forms. Thus, it would be premature to make any sweeping recommendations about calcium use as prophylaxis. Nevertheless, in view both of the cited studies and of the greater relative safety of calcium over estrogen, this alternative deserves more attention than Dr. Specht gave it.

In closing, it must be stressed that osteoporosis appears to be a very heterogeneous disorder, and that postmenopausal women themselves do not respond uniformly to any prophylactic intervention. No one regimen is likely to work for all, and it would be unrealistic to expect that it would. Nevertheless, as the practicing community faces the dilemma of how to approach prophylaxis in postmenopausal women, it must be said that calcium offers a number of attractive features.

ROBERT P. HEANEY, MD
Vice President for Health Sciences
Creighton University
Omaha, Nebraska

REFERENCES

1. Specht EE: Hip fracture, skeletal fragility, osteoporosis and hormonal deprivation in elderly women (Medical Progress). West J Med 133:297-303, Oct 1980

2. Recker RR, Saville PD, Heaney RP: The effect of estrogens and calcium carbonate on bone loss in postmenopausal women. Ann Intern Med 87:649-655, Dec 1977

3. Horsman A, Gallagher JC, Simpson M, et al: Prospective trial of oestrogen and calcium in postmenopausal women. Br Med J 2:789-792, Sep 24, 1977

4. Heaney RP, Recker RR, Saville, PD: Menopausal changes in calcium balance performance. J Lab Clin Med 92:953-963, Dec 1978

5. Matkovic V, Kostial K, Simonovic I, et al: Bone status and fracture rates in two regions of Yugoslavia. Am J Clin Nutr 32:540-549, Mar 1979

* * *

Dr. Specht Replies

To the Editor: I suspect that Dr. Heaney and I do not really have any fundamental differences regarding the desirability of calling the attention of the medical profession to this serious and unresolved problem. It is evident from both our works that we are laboring in the same vineyard.

I do take some exception, however, to certain of Dr. Heaney's statements. First, the comment that there is no clear relationship between bone mass and fragility. Dr. Heaney states, "Many women without hip fracture have no more bone mass than those with fracture. No one knows why this is so." I think this notion is a consequence of focusing too much attention on the altered physiology and not enough on the biomechanical aspects of fracture. The very same statement could be made, for instance, with regard to fractures of the femur in young athletes. Those who fracture their femurs playing football have no more bone mass than those who do not. The answer in both instances, of course, is that the unfractured bone simply has not yet had applied to it sufficient force to exceed its mechanical strength. There are obviously many variables in the application of stresses to bone and our comprehension of this entire area is currently rudimentary.

Second, Dr. Heaney states, "I believe it unlikely that the Food and Drug Administration will approve long-term, routine use of estrogen for the prevention of age-related bone loss in *unselected* postmenopausal women. . . ." This is very likely lamentable, everything, including proper dosage, considered. Furthermore, we do, in fact, have the methods to identify women at risk today, and additional screening techniques are in experimental stages at the present time. It is possible by utilization of photon absorptiometry with iodine 125 or americium 241 to determine bone mineral in vivo. Simpler although perhaps less accurate techniques, using radiologic measurements of cortical bone thickness have been described by Garn, Smith and Walker, and H. E. and S. Meema. Bloom and Laws have shown that combined cortical thickness of bone fell steadily after the age of 50 years, and this is, no doubt, yet another manifestation of the process which leads to skeletal fragility.

My apologia to Dr. Heaney for failing to cite his calcium balance studies in perimenopausal women is simply that there were many biochemical studies that I purposely avoided in my effort to concentrate on the biomechanical aspects of this problem. The paper as presented would not likely have been written by an internist, nor could I do a competent job in addressing the nuances of the biochemistry of this problem. There is no necessary correlation, after all, between alterations in calcium balance in postmenopausal women and ultimate skeletal fragility.

In my view there may well be a cause-and-

effect relationship, but it has not been satisfactorily demonstrated as yet, with the exception of the single study, cited by Dr. Heaney, of Matkovic and his co-workers in which a high calcium intake was, in fact, shown to reduce the incidence of hip fractures. I have no problem with utilizing any and all techniques for minimizing skeletal fragility in postmenopausal women. I do have some reservations, however, about accepting Dr. Heaney's final statement that "it must be stressed that osteoporosis appears to be a very heterogeneous disorder, and that postmenopausal women themselves do not respond uniformly to any prophylactic intervention. No one regimen is likely to work for all. . . ." If one excludes those types of osteoporoses related to immobilization, endocrine and hepatic causes, those that are heparin related, and other iatrogenic types, including radiation osteonecrosis, one is left with a definable group of postmenopausal women for whom estrogen replacement therapy does, in fact, work in the prevention of hip fractures. Hutchinson, Polansky and Feinstein showed this in a statistically validated study using exogenous estrogens to protect against fractures of the hip and distal radius. A protective effect was demonstrated with an odds ratio of 3.8 if administration was begun within five years of menopause.

In conclusion, I would state that I have no objection to whatever effective method an individual physician chooses to prevent the inevitable skeletal fragility and probable multiple fractures from which elderly women will almost assuredly suffer in time. The dilemma in my mind is not so much *how* to treat as it is the dire necessity of bringing to the attention of practicing physicians the overriding necessity of adequate prophylatic management. It is my belief that if we do not do something effective, this is another area which those who take pleasure in pillorying our profession will seize upon as an example of how we choose not to attempt to prevent disease, but only to treat after it has developed. I would not like to see the profession render any soupçon of substance to such an allegation.

ELMER E. SPECHT, MD
Professor of Orthopedics and Rehabilitation
University of Oregon Health Science Center
Portland

Refer to: Petrilli ES: Obstetrics and gynecology: Considerations in career selection. West J Med 134:77-79, Jan 1981

Special Article

Obstetrics and Gynecology: Considerations in Career Selection

EDMUND STEPHEN PETRILLI, MD, *Washington, DC*

Current training programs in obstetrics and gynecology are not producing an excess of specialists in view of future manpower needs. In addition to being specialists and consultants, obstetrician-gynecologists also function as providers of primary care for women. During the last decade, three formal subspecialties of obstetrics and gynecology have evolved: gynecologic oncology, maternal-fetal medicine and reproductive endocrinology. These have improved patient care and have altered the structure of resident education. With more American medical school graduates entering this specialty, the quality of resident applicants has improved, creating intense competition for desirable training positions. Those inclined toward a career in obstetrics and gynecology can be assured that it will provide an increasingly favorable and challenging environment for professional activity in the future.

FOR MANY MEDICAL STUDENTS, rewarding experiences during clinical clerkships result in attraction to particular areas of medicine and often form the basis for subsequent career selection. After personal interests are identified, students often consider issues that may affect them in the training and practice of a particular specialty. This report addresses some of the questions frequently asked by interested students regarding the present and future direction of obstetrics and gynecology. General influences include medical manpower requirements, distribution of physicians and ratios of specialists to generalists. More specific concerns involve the changing nature of specialty practice in obstetrics and gynecology, and the adequacy of current resident education to meet future needs. These considerations are important to all involved in the health care of women.

From the Department of Obstetrics and Gynecology, UCLA Center for the Health Sciences, Los Angeles. Dr. Petrilli is now affiliated with Georgetown University Hospital in Washington, DC.

Submitted, revised, June 23, 1980.

Reprint requests to: Edmund S. Petrilli, MD, Department of Obstetrics and Gynecology, Georgetown University Hospital, 3800 Reservoir Rd., N.W., Washington, DC 20007.

Manpower Requirements

The 78th Annual Report on Medical Education of the *Journal of the American Medical Association* provides an extensive analysis of the past, present and future status of medical manpower.[1] Between 1960 and 1977 the number of medical students graduating annually doubled from 7,000 to 14,000 and medical schools increased from 86 to 124 in response to the need for more doctors in the United States. The growth rate of new physicians, five times higher than that of the general population, has since begun to decline

and will stabilize in the 1980's with 16,000 to 17,000 graduates each year. There were 437,000 physicians in this country at the end of 1977, of which 192,629 held specialty certificates—including 14,199 in obstetrics and gynecology. The lack of adequate health care services that persists for certain segments of the population is no longer due to an insufficient number of physicians. Such deficiencies exist because of an imbalance in the proportion of specialists to generalists, and poor geographical distribution of physicians in relation to health care needs.[2] The goal of having at least 50 percent of all medical graduates train in areas of primary care is being successfully reached, given the stimulus of government support. Inadequate distribution of physicians continues to occur in rural and inner city locations, however, where the lowest physician to patient ratios exist. Finding a solution to this problem may be more difficult than altering the ratio of specialists to generalists.

There is some concern that more physicians are being trained in obstetrics and gynecology than will be needed in 10 or 20 years. This is unlikely, however, because it has been projected that 32,000 to 40,000 such specialists will be needed by 1990 when the estimated supply will not exceed 32,000.[3] The demand for services may increase at a faster rate than the population because it is expected that more people will participate in the health care system in the future. Thus, the subsequent demand for obstetric-gynecologic care could exceed available resources despite a projected increase in the ratio of specialists to the population. For example, although the birth rate has declined, obstetricians are now responsible for 81 percent of all deliveries in comparison to only 68 percent a decade ago as a result of decreasing participation by general practitioners.[4] This suggests that the potential work load for each obstetrician should at least remain stable in the future barring unexpected changes in projected birth rates. Other areas of patient care involving family planning, cancer screening and minor gynecologic problems will require more sharing of responsibility in the future. Generalists, internists and nurse practitioners could also provide this care, particularly in rural or inner city locations, if demands reach the higher range of projections. However, it is unlikely that the number of trained obstetrician-gynecologists will exceed the needs of this country during the next 20 years.

Nature of the Specialty

There has been controversy regarding the nature of the health care provided by obstetrics and gynecology. In addition to providing specialized medical services, it is also a unique source of primary care for women. Willson and Burkons[5] found that 86 percent of women surveyed visited no physician other than their obstetrician-gynecologist on a routine basis; 25 percent had conditions diagnosed that were unrelated to the specialty. Fifty percent of the responding doctors commonly treated health problems unrelated to obstetrics and gynecology. This dual form of care appears to be rewarding to these practitioners. Wechsler and co-workers[6] reported that 74 percent of obstetrician-gynecologists practice their specialty at least half-time, ten years after the completion of training, in comparison to 56 percent of pediatricians and 28 percent of internists.

During the past decade three areas of formal subspecialization have evolved within obstetrics and gynecology in an attempt to incorporate rapid scientific progress and to provide optimal training, research and patient care. These are gynecologic oncology, maternal-fetal medicine and reproductive endocrinology. Approximately 2 percent of obstetrician-gynecologists have subspecialty certification at present, compared with 35 percent of internists.[7] It is estimated that the needs of society could be met if 10 percent of all obstetrician-gynecologists were certified subspecialists.[8] The desired representation in maternal-fetal medicine and reproductive endocrinology may not be reached in the foreseeable future. Referral centers, which are responsible for teaching, research and patient care have the greatest need for certified subspecialists. Subspecialty divisions within departments of obstetrics and gynecology have effected changes in the structure and content of residency programs, resulting in a more concentrated approach to the treatment of patients with complicated diseases. Whether or not this advantage compensates for the shift of some degree of resident responsibility to the fellowship level is controversial. One example of this influence on subsequent patterns of practice is that recent graduates of residency programs tend to refer more complex clinical problems to tertiary centers than practitioners who completed training before the era of formal subspecialization.[9] The

central issue in such matters is the recognized obligation to deliver optimal care to women with special health problems, rather than where or by whom this care is provided.

Resident Education

The number of training positions in obstetrics and gynecology has remained fairly constant over the last decade and about 7 percent of American medical school graduates continue to enter the specialty each year.[10] In 1977-1978 there were over 4,000 residents training in obstetrics and gynecology. In recent years about 30 percent of new house officers have been women, which reflects their increasing representation in medical schools rather than a disproportionate interest in the specialty.[11] The increasing number of American graduates entering residency programs has resulted in the acceptance of fewer graduates of foreign medical schools and greater competition for the available training positions (personal communication, February 1979, Council on Resident Education in Obstetrics and Gynecology Data Bank, One East Wacker, Chicago, IL 60601).

Willson and Burkons[9] found that 72 percent of the specialists trained in university programs considered themselves well prepared for practice in comparison to only 45 percent of those trained in community hospitals. The failure rates on both the written and oral parts of the American Board specialty examination are higher for the latter group. Good community hospitals may need to become more closely affiliated with university centers to strengthen their training capabilities and marginal educational programs may deteriorate further and cease to function. University and affiliated programs, maintaining a higher quality of education than exists elsewhere at present, could efficiently meet future training needs as they occur. This projection is in keeping with the recent emphasis on regionalized patterns of care. University departments will also be expected to provide additional training for residents in family practice programs. These physicians will be needed in the future to provide the ambulatory services beyond those that can be delivered by obstetrician-gynecologists.

Traditionally, training programs have stressed the specialist-consultant aspects of obstetrics and gynecology. Some suggest that the realities of practice demand more educational exposure to other primary care disciplines.[9] Additional core experience in abdominal and pelvic surgical procedures is advocated by others.[12] An eventual restructuring of the basic residency program could be forthcoming as a result of these considerations.

In 1978 there were 188 applications for residency submitted to the Department of Obstetrics and Gynecology at the University of California, Los Angeles; 120 candidates were interviewed. Six positions were filled from within the first 20 applicants listed with the National Interns and Residents Matching Program. The criteria used in resident selection included National Board examination scores, academic honors, letters of recommendation and personal interviews. Many educators hold the opinion that the quality of resident applicants has improved substantially in recent years, however, the deletion of standard objective criteria such as grades and class rank makes this impression difficult to quantitate.[7,10,11]

When questioned about their choice of obstetrics and gynecology as a career, most candidates related an interest in the combination of specialized medical and surgical skills and the opportunity to provide primary and continuing patient care. This is consistent with the dual practice role of obstetrician-gynecologists and correlates with subsequent career satisfaction. Many persons are attracted to the exciting research horizons offered by the subspecialties in obstetrics and gynecology, which have become highly competitive with other areas of medicine. A favorable and challenging professional environment can be expected by those considering future careers in this specialty.

REFERENCES

1. The 78th Annual Report on Medical Education in the United States. JAMA 240:2810-2814, 1978

2. Wechsler H: Selecting a specialty. New Physician 25:41-43, May 1976

3. Peckham BM: Resident training goals in obstetrics and gynecology for the 1980's. Am J Obstet Gynecol 132:709-716, 1978

4. Pearse WH: Who delivers babies (Editorial). ACOG Newsletter 23:3, May 1979

5. Willson JR, Burkons DM: Obstetrician-gynecologists are primary physicians to women—I. Practice patterns of Michigan obstetrician-gynecologists. Am J Obstet Gynecol 126:627-632, 1976

6. Wechsler H, Dorsey J, Bovey JD: A follow-up study of residents in internal medicine, pediatrics and obstetrics-gynecology training programs in Massachusetts. N Engl J Med 298:15-21, 1978

7. Pearse WH, Trabin JR: Subspecialization in obstetrics and gynecology. Am J Obstet Gynecol 128:303-307, 1977

8. Trabin JR, Pearse WH, Carter R: Subspecialization manpower in obstetrics and gynecology. Obstet Gynecol 51:494-498, 1978

9. Willson JR, Burkons DM: Obstetrician-gynecologists are primary physicians to women—II. Education for a new role. Am J Obstet Gynecol 126:744-754, 1976

10. Pearse WH: Doctors and patients in obstetrics and gynecology: The next 15 years. Am J Obstet Gynecol 125:361-367, 1976

11. Douglas GW: Centennial insights. Am J Obstet Gynecol 126:739-743, 1976

12. Lewis JL, Barber HRK, Boronow RC, et al: What's wrong with ob-gyn surgical training?—How can it be upgraded? Contemp Gynecol 14:78-102, 1979

Refer to: Fremont AC, Wallace HM, Crain L, et al: Medical and health care in state residential institutions for children and youths: A report of survey findings in five hospitals —The Committee on Children With Handicaps, Northern California Chapter, American Academy of Pediatrics (Health Care Delivery). West J Med 134:80-86, Jan 1981

Medical and Health Care in State Residential Institutions for Children and Youths

A Report of Survey Findings in Five Hospitals

The Committee on Children With Handicaps, Northern California Chapter, American Academy of Pediatrics

ALBERT C. FREMONT, MD, MPH, Chairman; HELEN M. WALLACE, MD, MPH, Subcommittee Chairman; LUCY CRAIN, MD, MPH; KRIST A. BIAKANJA, MD, *and* NANCY ROIZEN, MD

A survey of five Northern California state residential institutions showed considerable variation in the type and amount of medical services provided for children and youths. There was no standard policy for relationships with regional centers, use of community hospitals, vision and hearing assessments, speech and rehabilitation therapy, or genetic and maternal health services. Some hospitals had no staff members certified to carry out cardiopulmonary resuscitation (CPR). Not all staff physicians and other health professionals working in state hospitals had specific training in the areas of genetics, seizure control and physical rehabilitation medicine. While all five state hospitals are involved in training personnel, there is a need to develop a statewide plan for the better sharing of knowledge and expertise of the state hospital personnel in the training of pediatricians and others.

In 1973 a subcommittee of pediatricians from the Committee on Children with Handicaps of the Northern California Chapter of the American Academy of Pediatrics, chaired by Dr. Peter Cohen, was invited by the Director of the California State Developmental Disabilities Program to visit a major state residential institution for the handicapped in Northern California in order to help define areas of concern and to suggest ways to improve health care of children in this facility. At that time the group found (1) too few staff physicians to provide a high quality of care for patients, (2) lack of availability of medical and surgical consultants, (3) low staff morale, (4) a backlog of patients requiring elective surgical procedures, caused by the closing down of the surgical unit, (5) inadequate dental care, (6) inadequate occupational and physical therapy, (7) inadequate information from some of the referral centers for optimum planning for the care of patients upon admission, and inadequate information from the state hospital to agencies upon the discharge of patients.

Reprint requests to: Albert C. Fremont, MD, Child and Adolescent Neurodiagnostic Clinic, Santa Clara Valley Medical Center, 751 S. Bascom, San Jose, CA 95128.

ABBREVIATIONS USED IN TEXT

CPR = Cardiopulmonary resuscitation
IEP = Individual education plan
JCAH = Joint Commission on Accreditation of Hospitals

These findings were conveyed to the state institution and to the Director of the Developmental Disabilities Program in the California State Department of Health.

In response to the 1973 subcommittee report, physician salary scales were increased and all budgeted positions were filled. An important result of the review was that guidelines were set up for billing Medi-Cal on a fee-for-service basis for necessary medical care obtained in the community by state hospital residents. This change enabled state hospital residents to benefit from mainstream health care resources and also made adequate specialty consultation possible.

The result was a prompt improvement of state hospital physician and staff morale. A number of program improvements followed. By referring surgical and acute medical problems to a local community teaching hospital, the hospital waiting list for elective operations was eliminated. A central dental clinic was established and efforts were made to deliver more adequate dental hygiene care as well as corrective dentistry. "Budgetary restrictions" of that time were cited as the reason why physical and occupational therapy services were not increased.

In 1978 members of the Northern California Chapter of the American Academy of Pediatrics again visited state residential institutions in Northern California to reassess the status of medical and health care of children and youths. This survey, also initiated by the Committee on Children with Handicaps, was expanded to include all five Northern California state hospitals, including the one reviewed in 1973. The 1978 survey group decided to include other areas of care in their review, such as rehabilitation, speech and language therapy, genetic services, maternal health care, special education, vision and hearing assessment, and laboratory and emergency services.

Methods

An appointment was made with each of the five state hospital administrators well in advance. A survey outline provided a systematic review of the major areas of patient care, such as census and population; number and specialty of medical staff; admission procedures; patient workup and evaluation procedures; acute care, emergency surgical, laboratory and radiologic facilities; maternal health care; genetic services; vision, hearing and speech therapy; care of patients with seizures; dental health care; education; rehabilitation, and recreation. A meeting was held with the administrator, the director of medical services, and usually the program directors of the childrens' services. A tour was made of the services for children and youths. As the survey was being completed, the staff were asked for their suggestions and recommendations.

In addition to the data secured from the administrator and the professional and technical staff of each of the institutions at the time of the visit, some information was obtained by a follow-up telephone call to the administrator after the visit. The survey committee is very grateful to the administrators and staff of the state residential institutions for their cooperation and assistance.

Only one visit was made to each residential institution.

Results

Administration

The five state residential institutions surveyed were large (with total capacities varying from 750 to 2,079). With the exception of two hospitals, all institutions were filled to capacity.

Half the total occupancy in two institutions was set aside for children and youths. In two others a fourth of the total, and in the fifth institution a sixth of the total occupancy was for children and youths. The census of children and youths was approximately half of the beds available, varying from 90 to 650 (Table 1).

Three of the five state residential institutions are accredited by the Joint Commission on Accreditation of Hospitals (JCAH), and two are not.[1] Patient cost per day for children and youths ranged from $60 to $150. Higher rates were reported from hospital wards providing acute hospital care.

The children and youths cared for in these five residential facilities are developmentally disabled, that is, they are diagnosed as having cerebral palsy, mental retardation, epilepsy, autism, or a combination of these disabilities. Some are very severely retarded and some are very severely physically disabled. In several institutions there

are some youths and children who are emotionally disturbed.

Four of the five residential institutions had no children and youths on a waiting list. The fifth had a small waiting list (four or five), and the waiting period was as long as one year.

Children and youths are admitted to all five residential institutions through the 21 regional centers for the developmentally disabled, and in two institutions they are also referred by community mental health centers.

A team, usually consisting of a physician and social worker, and often including a psychologist, teacher, physical therapist, dentist or nurse see the child or youth upon admission to hospital or within 30 days of admission (Table 2). The physician is usually not a pediatrician. One institution arranges a preadmission visit for each potential resident during which the patient and his or her family can meet the program physician, hospital director and social worker.

Relationship With Regional Centers

All institutions reported lack of uniformity in the quality and quantity of patient information provided to them by regional centers before a patient's admission. They mentioned the need for agreement on minimum acceptable standards for preadmission information. Material most frequently lacking was a medical history, a medical examination and a psychology consultation.

Several institutions reported the need for a much closer relationship between the regional centers and the state institutions. They felt the staff of the regional centers should attend staff conferences at the state institution when an individual patient was reviewed, and that staff of both the regional center and the state institution should meet more frequently to discuss mutual problems.

Records

All institutions visited maintained problem-oriented, chronologically continuous records for each resident. Records were not consistent because the amount of preadmission information received from admitting agencies (that is, regional centers or community mental health services, or both) varied. The lack of standardized preadmission information as well as minor variations in record systems at different hospitals often made it difficult for the review group to retrieve basic health maintenance information on children, such as immunization status and history of childhood infectious diseases.

TABLE 1.—*Capacity and Census of Children and Youths, and Medical Staff of Five Northern California State Residential Institutions*

Institution	Total Capacity	Total Census	Children and Youth				Medical Staff		
			Capacity	Census	Type	Age	All Medical Staff	Vacancies	Pediatricians
A	1,900-2,000	1,900	1,100	650	DD	Under 21	21	0	5
B	1,850	1,844	450	195	A, BD, DD, ED	Under 19	72	20	1 (PT)
C	1,200	930-936	203	138	DD	Under 18	11*	1	1
D	750	750	180	90	DD	Under 21	21†	0	1†
E	2,079	1,630	1,000	500	DD, SR§	Under 21	22‖	1	4*

A = autistic; BD = brain damaged; DD = developmentally disabled; ED = emotionally disturbed; PT = part-time; SR = severely retarded

*One part-time employee.
†11 state, 10 county employees.
‡State employee.
§Some ambulatory, some severely disabled.
‖Includes five part-time employees.

TABLE 2.—*Who Sees Children and Youths on Admission*

Institution	Pediatrician	Social Worker	Teacher	Other Physician	Nurse	Other
A	X	X	X		X	Rehabilitation worker, physical therapist, occupational therapist
B		X				
C		X	X	X	X	Rehabilitation therapist, psychologist, group leader, counselor
D		X		X		Dentist, program director, psychologist, physical therapist
E		X	X	X		Psychologist, dentist

Medical Staff

The medical staff of the state residential institutions consists of a number of full-time physicians, board-eligible or board-certified specialists, including specialists in psychiatry, internal medicine, surgery (including orthopedic surgery), otolaryngology, ophthalmology and obstetrics and gynecology. All five state residential institutions have at least one pediatrician, although one institution with 450 children and youths has only one part-time pediatrician. Pediatricians make up only a small proportion of the total medical staff (7.7 percent), although children and youths represent a considerable proportion of the resident patient load (22.3 percent) (see Table 1).

Periodic Evaluation and Screening of Children and Youths

In at least four of the five institutions, children and youths are reviewed or examined, or both, at least once a year; in four of these five, twice a year. All five institutions use problem-oriented records.

Vision and Hearing Services

All five institutions have an ophthalmologist, usually one who works part-time. All five have an eye clinic. In four of the five institutions, children and youths receive a vision screening on admission and vision screening annually. This may be done by a technician, nurse or physician.

All five institutions have an otolaryngologist, usually one who works part-time.

In the four institutions that have an audiologist, hearing screening of children and youths is done on admission; three repeat it a year later. Screening is usually done by a technician, nurse or audiologist. Two institutions reported referring children and youths to a nearby university for hearing evaluation. One institution reported a long waiting list for evaluation of residents suspected of having hearing or language deficits, or both. Two other institutions reported needing a larger speech therapy staff. (All institutions employed a speech therapist.)

Dental Health Care

All state institutions have at least one dentist, four have a dental hygienist and four have at least one dental assistant.

One institution reported having a consultant for oral surgery and operative dentistry; in that institution, dental surgical procedures are done in a community hospital.

One institution reported having a nurse anesthetist employed exclusively for the dental program.

Institutions provided cleaning, filling and extraction of teeth. The institutions usually made it possible for a member of the dental health staff to see a new patient within 30 days and to see patients periodically thereafter, usually annually.

Data on the ratio of decayed, missing and filled teeth in residents were not available.

Maternal Health Services

All five state institutions have at least one part-time obstetrician/gynecologist, two have at least one full-time obstetrician/gynecologist.

Four of the five state institutions had a committee on sex education and family planning; the fifth used ward staff members interested in providing sex education. Abortions and sterilizations, if necessary, are performed by community health care providers outside the state institutions. There are very limited family planning (contraception) services within the state institutions. Pregnancy is uncommon.

Genetics Services

One of the five institutions provides a partial genetics counseling service, consisting of a genetics clinic quarterly, and use of a medical consultant from time to time. A second institution sends its patients to a genetics center in a nearby medical school. A third institution reported that it uses a community hospital for laboratory work. The other two institutions provide no service.

Management of Patients With Seizures

All five state institutions reported that patients with seizures represent a significant percentage of the total resident population, varying from 10 percent to 60 percent. There are no special provisions for these patients. The ward physician manages patients' seizures as he or she would manage any other medical problem. All institutions reported that they had a core of patients whose seizures are difficult to control. The use of laboratory tests to monitor levels of anticonvulsant drugs in the blood varies. All five state institutions have a consulting neurologist.

Affiliation With and Use of Community Hospitals

All five state institutions refer residents to local community hospitals for one sort of care or an-

other. Two state institutions refer patients to community hospitals for major operations and two for dental surgical procedures. At least two state institutions refer patients with seizures to community hospitals. One state institution reported referring patients to a community hospital for genetic laboratory tests; another for labor and delivery of pregnant women, if the patient's family agrees.

Major Surgical Operations

Two of the five state institutions carry out major operations on the premises, while the other three refer patients to nearby community hospitals. Several of the state institutions mentioned the problem of providing an adequate anesthesiology staff and service. All of the state institutions have at least one consulting surgeon on their staff.

Laboratory Services

Four of the five institutions have laboratory services that perform urine and blood analyses. Three of the five are able to do laboratory determinations to monitor blood for anticonvulsant drug levels.

Rehabilitation Services

A significant proportion of the patient populations of most of the five state institutions visited are severely physically disabled. No institution had a physiatrist on the staff or as a consultant. One reported the availability of a physiatrist, who is rarely used, at a nearby county hospital. Three institutions reported that they had a part-time orthopedic surgeon on the staff. Four of the state institutions employed at least one physical therapist.

Two institutions reported having a speech therapist and one of these two has an audiologist; the other of these two had a speech pathologist. In addition, one institution reported having a music therapist, one a dance therapist, one a developmental specialist and one a rehabilitation therapist. Three of the five state institutions had several rehabilitation staff members. Physical, occupational, speech and rehabilitation staff members usually receive patient orders and prescriptions from the ward physicians, who have not had training in physical rehabilitation.

Several of the state institutions reported having a problem filling vacancies on their therapy staffs. They attributed this to the location of the institution, working conditions and the environment, and salary—which were described as being noncompetitive with private hospitals or private practice.

Four of the five state institutions have a sheltered workshop, primarily for adults. Three institutions have prevocational training. The vocational services are for adults rather than for teenagers.

Cardiopulmonary Resuscitation

All hospitals reported that staff were involved in obtaining cardiopulmonary resuscitation (CPR) training and certification. The number of staff members who already had certificates varied considerably among the hospitals (exact statistics were not obtained). The committee was concerned about the variation in ward staff attitude regarding the handling of emergencies and the access to emergency equipment and support staff. This ranged from the situation in one hospital where well-stocked emergency "crash carts" were immediately accessible on high-risk wards, with all staff trained in CPR, to another hospital where makeshift emergency equipment located at the nursing stations was apparently accessible only to certain trained staff who were not always available.

Staff at one hospital complained of an antiquated in-hospital telephone system, which, because of its frequent dysfunction, could make it impossible to contact needed CPR personnel in the event of an emergency. Another hospital, where most of the staff were already trained in CPR, provided belt-clip portable pagers to be worn by all on-call personnel to insure prompt availability. The lack of standardization of acceptable emergency procedures, equipment and personnel lends a sense of confusion to this important area. In some institutions it seemed possible that some staff were unable to distinguish those CPR procedures needed immediately from those that were handled in the hospital emergency room or referred to a local community hospital. This suggests the need for more emergency (that is, CPR) training for all program personnel.

Role of the State Institutions in Training

All five state institutions are involved in training. Two institutions are training medical personnel—one, residents in physical medicine and rehabilitation, another, residents in child psychiatry. A third institution is working on a plan for training residents in psychiatry. At two institutions

interest was expressed in having residents in pediatrics, and at one in having residents in medicine.

Four institutions are engaged in training other personnel, including physical therapy students (three), technicians, medical records librarians, recreation therapists, teachers and psychiatric technicians.

Education

Four of the five state institutions send a few children to schools in the nearby community. All five state institutions have a school on the grounds. One institution had no program for children and youths with learning disorders.

Two of the five state institutions had submitted a plan for implementation of Public Law 94-142, the Education of All Handicapped Children Act. Several reported the need for more staff. More than one institution had special problems with residents aged 18 to 22 years. One reported the need to involve the parents more. Two reported the need to develop an individual educational plan (IEP) for each child.

Discussion

One important question is whether each state hospital should be equipped and staffed to provide the complete spectrum of inpatient residential services, or whether a California statewide or a regional plan should allocate certain more specialized services to one or more specific hospitals. The State Department of Developmental Disabilities Services has already taken steps to resolve this issue for patients needing major surgery, by advocating the extensive use of community hospitals, thereby enabling some hospitals to phase out surgical services. Better regional and statewide planning might facilitate more appropriate use of resources, concentrating certain services in one or more hospitals, such as skilled nursing care and physical rehabilitation for the severely physically disabled.

Each state residential institution must review the situation and develop methods that strengthen the working relationship of the institution with medical schools and teaching hospitals. Ties with hospitals would enable the institutions to use consultants in the case of seriously ill or potentially seriously ill patients.

Each state residential institution should provide basic laboratory services as well as more sophisticated laboratory tests, such as those that monitor medications for patients with seizures. Microchemical techniques should also be available.

The role of state residential institutions in regard to the training of undergraduate, graduate and postdoctoral students in the health professions, must be clarified. Specifically, can a state residential institution take the initiative in this area instead of depending on a formally arranged plan with a base university or other educational facility? The assignment of students and postdoctoral trainees to a state residential institution requires teaching and supervisory staff from both the base institution and the state residential institution.

A plan for obtaining consistently thorough information from the regional centers before admission of a patient should be formulated. Liaison between institutions and regional centers should allow for frequent conferences about patients, and, in turn, the state residential institution should provide the regional center with complete records when a patient is discharged. There is a real need for standardization of medical and psychological background information provided to an institution when a patient is admitted.

What genetics services should the institutions provide? A policy regarding these services would be useful. A consultant in genetics from a medical school or teaching hospital should be employed to set up genetic diagnostic services, laboratory services, counseling, follow-up with families, and the introduction of family planning information and services where appropriate.

Another area requiring review is that of sexuality—sex education and family planning. It is suggested that policies be set for the state residential institutions as a whole, and the program be reviewed by each state residential institution. This includes providing sex education and teaching the patients regarding maternal health care (prenatal, postpartum), care of the baby and child, family planning and abortion.

Many of the residents in the state residential institutions are severely disabled. Plans for strengthening the rehabilitation services are needed, including the employment of a qualified physiatrist to direct and supervise the program, the therapy staff and patients' prescriptions. Here, too, liaison with medical schools and teaching hospitals would be useful.

Also, who should be responsible for a program

to manage patients with seizures in each institution? Would an in-service training program on this subject be useful, and at whom should such a program be directed?

Institutions must re-examine the composition of the medical staff, particularly with regard to the type of physician responsible for basic medical care of the patients. Should there be pediatricians for the children and youths, and internists for the adults? It would appear that some type of formula should be set for the ratio of pediatricians needed on the staff for the children and youths in the institution. Some institutions visited had far too high a patient to physician ratio.

Vision and hearing screening, follow-up and patient care programs are in need of revision. Each patient should have vision and hearing screening on admission and annually thereafter. Standards are needed for visual and auditory tests. Moreover, which staff members should do the screening?

To implement Public Law 94-142, an individual educational plan must be made for each child and youth. Taking parents' ideas into account, this plan should be part of the basic program of medical, social and rehabilitation care provided for each child and youth. Vocational services are part of the educational needs of a youth and so should be included in such plans.

In view of the extensive scope of this survey, the major area of mental health services for emotionally disordered and behaviorally disturbed children and youths with developmental disabilities was not dealt with in adequate depth. We realize that this is an important area that requires a much more intensive review and report. This might well be the subject of a subsequent survey by this committee.

The committee initially referred to the standards of the JCAH which has established general guidelines in the area of physical development and health. Because of the very general nature of these standards, the committee also addressed certain areas in greater depth. Further thought should be given to the need for more specific standards in health care.

REFERENCE

1. Joint Commission on Accreditation of Hospitals (JCAH): Standards for Services for Developmentally Disabled Individuals. Chicago, JCAH, 1978

Allergy Problems From 'Hidden' Corn

CORN SEEMS TO BE an ingredient of almost everything. You can find it as a flour, a meal, an oil, a sugar, a syrup and in your IV solutions. Do not forget that the sugar in almost all IV solutions is corn; if you have a severely corn-allergic patient, you would not want to give him his allergic food intravenously. Our corn-allergic patients are instructed to call us if they are going to have an operation and we get the anesthesiologist to start his induction with plain saline. . . . The three main sugars in this country are corn, beet and cane. . . . The most commonly used commercial sugar is corn. Manufacturers of foods are only required to list "sugar" on their labels, and they will fox you—they sometimes use one kind of sugar at one time of year and another kind at the other time. The poor patients read "sugar" and cannot tell which kind it is. Therefore, patients who have a corn, cane or beet allergy just cannot eat commercial products that say "sugar" on the label.

—JOHN H. BOYLES, Jr, MD, *Dayton, Ohio*

Extracted from *Audio-Digest Otorhinolaryngology*, Vol. 13, No. 15, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1577 E. Chevy Chase Drive, Glendale, CA 91206.

Refer to: Simon RP: Neurosyphilis: An update (Information). West J Med 134:87-91, Jan 1981

Information

Neurosyphilis: An Update

ROGER P. SIMON, MD, *San Francisco*

SEVERAL RECENT STUDIES[1,2] and reviews[3] have suggested that neurosyphilis remains an important and frequently encountered entity. The incidence of late and late-latent syphilis in California from 1974 to 1977 averaged 30 cases per 100,000 persons (written communication, State of California Department of Health, Venereal Disease Control Unit, December 1979). Of these, approximately one case in ten would be expected to be symptomatic neurosyphilis[4]—that is, three newly symptomatic cases of neurosyphilis per 100,000 population represents all cases, the current probably represent only a fraction of the actual incidence, but if one assumes that three per 100,000 population represents all cases, the current incidence of neurosyphilis is similar to that of Huntington chorea, double that of amyotrophic lateral sclerosis, about half that of multiple sclerosis and a seventh that of Parkinson disease.[5,6]

Clinical Spectrum

The frequency and clinical spectrum of neurosyphilis have been documented by Hooshmand[1] from the University of Virginia Hospitals. He reported 241 cases diagnosed between 1965 and 1970.[1] The criteria for diagnosis were (1) a positive FTA-ABS (fluorescent treponemal antibody absorption) test with ocular or neurological findings suggestive of neurosyphilis, (2) reactive serum and spinal fluid FTA-ABS tests with more than 5 lymphocytes per cu mm in cerebrospinal fluid (CSF) or (3) positive FTA-ABS tests in blood and spinal fluid in patients with otherwise unexplained progressive neurological disease in whom penicillin therapy either resulted in significant improvement or produced a transient CSF pleocytosis.

ABBREVIATIONS USED IN TEXT

CNS = central nervous system
CSF = cerebrospinal fluid
FTA-ABS = fluorescent treponemal antibody absorption (test)
TPI = *Treponema pallidum* immobilization (test)

The signs and symptoms observed in Hooshmand's series of patients are summarized in Tables 1 and 2. The most common presentation was some unrelated symptom, the diagnosis being made only on routine serological tests; abnormal reflexes or eye signs, or both, compatible with neurosyphilis were noted during evaluation of the reactive serological findings. Of the more specific neurological symptoms, focal or generalized seizures were most common and were usually associated with some other evidence of neurosyphilis. Other common abnormalities included disorders of vision or oculomotor function, dizziness, confusion and stroke. Psychiatric presentations were responsible for only 2 percent of cases in this series.

Although abnormalities on neurological examination were found in more than 75 percent of patients, these were most often nonspecific; for example, reflex changes were noted in 75.8 percent and absent ankle jerks in 66.8 percent of the patients. Of greater value was the evidence of posterior column sensory loss detected in 33.7 percent of the cases. Pupillary abnormalities of some degree (small irregular pupils, absence of light reaction, synechiae or light-near dissociation) were noted in about 45 percent of the cases. Ptosis, occasionally an isolated finding, was noted in nearly 5 percent of cases and felt by the authors to be a minor aspect of tabes dorsalis.

Pertinent laboratory studies in Hooshmand's series of patients included reactive FTA-ABS tests of blood and spinal fluid specimens in 100 percent of the cases, whereas nontreponemal tests were positive in less than 50 percent of serum and 6 percent of CSF specimens. The CSF protein level was normal in greater than 60 percent of cases, and nearly 20 percent of patients had less than five leukocytes per cu mm in the spinal fluid. The CSF gamma globulin fraction was elevated in about 66 percent of the patients examined.

The prognosis of the patients following therapy varied with the presenting symptoms, being poorest in those with clinical features of GPI (general

From the Department of Neurology, San Francisco General Hospital, and University of California, San Francisco, School of Medicine.

Reprint requests to: Roger P. Simon, MD, Neurology Service (4M62), San Francisco General Hospital, San Francisco, CA 94110.

paresis of the insane; dementia paralytica) in combination with seizures, and best in patients with stroke or adult-onset seizures.

Although the epidemiologic and clinical data reviewed above suggest that central nervous system (CNS) syphilis remains a current medical problem, classic cases of tabes dorsalis, general paresis and meningovascular syphilis are uncommon on hospital wards. At the San Francisco General Hospital Neurology Service we saw only 28 such cases between 1970 and 1978.

TABLE 1.—*Signs of Neurosyphilis**

Signs	*Number*	*Percent of Cases*
Reflex changes	183	75.8
Absent ankle jerk	161	66.8
Pupil changes	86	44.8
Sensory abnormalities	57	33.7
Chorioretinitis, retinitis pigmentosa	29	12.0
Organic brain syndrome	21	8.7
Babinski sign	13	5.3
Depression	12	5.0
Ptosis	11	4.6
Optic atrophy	11	4.6
Mania	8	3.3
Personality changes	5	2.0

*Adapted from Hooshmand et al.[1]

TABLE 2.—*Symptoms of Neurosyphilis**

Symptoms	*Number*	*Percent of Cases*
Seizures		
Focal	10	4.2
General	24	10.0
Not specified	24	10.0
TOTAL	58	24.2
Ophthalmic symptoms	28	11.6
Stroke: confusion	27	11.1
Dizziness	19	7.9
Personality changes	5	2.0
Unrelated symptoms	104	43.2
TOTAL	241	100.0

*Adapted from Hooshmand et al.[1]

TABLE 3.—*Serological Tests for Syphilis*

Nontreponemal tests
- Flocculation
  - VDRL (Venereal Disease Research Laboratory)
  - Hinton
  - Rapid reagin
- Complement fixation
  - Kolmer

Treponemal tests
- TPI (*Treponema pallidum* immobilization)
- FTA (fluorescent treponemal antibody)

Several authors have suggested that the clinical presentation of central nervous system syphilis has been altered in the era of antibiotic drugs. It is true that the large numbers of cases of tertiary syphilis that had been expected to result from the documented primary and secondary cases acquired during the Second World War have not occurred.[7] The role of antibiotic therapy in the lack of progression of those infections seems certain; disease modification versus cure following such therapy, however, has not been conclusively documented. Luxon and co-workers,[8] discussing the clinical presentation of CNS syphilis, found no evidence for modified clinical presentations in their 17 recently diagnosed cases. They noted that the presentations were diverse but that all clinical phenomena had been reported in the era before antibiotic therapy.

Pupillary abnormalities remain the most common clinical clue, but the diagnosis remains difficult in many cases. Increased reliance must therefore be placed on serological tests.

Serological Diagnosis

The serological tests for syphilis are treponemal and nontreponemal (Table 3). The nontreponemal tests detect nonspecific antibodies (reagins) that react with lipoidal antigens of *Treponema pallidum* or lipoidal antigens secondary to treponemal host interaction. The most commonly used nontreponemal test is the VDRL. This test relies on the ability of syphilitic serum containing reagin to flocculate a suspension of cardiolipin-lecithin antigen. Unfortunately, this nonspecific antibody (reagin) may also be present in collagen-vascular disease, after febrile illnesses, following immunization, in leprosy or in association with old age and in drug addiction.[9] Most important, however, this test is relatively insensitive in tertiary disease producing a nonreactive VDRL response in as many as a fourth of the cases of late syphilis.[10] In Hooshmand's series, for instance, reagin tests were positive in only 40 percent of cases.

The treponemal tests detect antibodies specific for *T pallidum*. The most widely used is the FTA-ABS test in which the patient's serum is first diluted in a "sorbent" prepared from a nonpathogenic treponeme to minimize false-positive tests and then is layered on a slide coated with dried *T pallidum*. Slides are incubated and then treated with fluorescent-labeled antibody to human gamma globulin. Fluorescence of the dried treponeme organisms indicates antitreponemal anti-

bodies in the patient's serum. This test is clearly more specific and sensitive than the VDRL test; however, it is technically much more difficult to carry out and some variation from laboratory to laboratory has been reported, especially in weakly reactive specimens.[9] In addition, while the quantitative VDRL test shows a falling titer in response to antibiotic therapy, except in so called "serofast" cases, the FTA-ABS test remains reactive indefinitely and therefore is not helpful in documenting a response to therapy. The most important distinction between these two tests in regard to tertiary disease is that the FTA-ABS test remains reactive in greater than 95 percent of patients with late syphilis and therefore greatly assists in the diagnosis of atypical presentation of CNS involvement (Table 4).[10]

In questionable cases an additional specific treponemal test is occasionally used in reference laboratories. This *T pallidum* immobilization (TPI) test detects serum antibodies to *T pallidum* by noting under the microscope a decrease in motility of live organisms when treated with the patient's serum. The study is technically difficult to carry out and not widely available although it is quite specific. Like the FTA-ABS test, it remains positive following treatment.

TABLE 4.—*Comparative Reactivity of Serological Tests**

Condition	*Number*	*Percent Reactive to Tests*		
		FTA-ABS	*TPI*	*VDRL*
Primary syphilis	191	85	56	78
Secondary syphilis ...	270	99	94	97
Late syphilis	117	95	92	77
Latent syphilis	954	95	94	74
Presumably normal ...	384	1	0	0

FTA-ABS = fluorescent treponemal antibody absorption; TPI = *Treponemal pallidum* immobilization; VDRL = Venereal Disease Research Laboratory

*Adapted from Sparling.[10]

Cerebral Spinal Fluid Tests

Continued attention to the testing of CSF specimens for evidence of syphilis is the result of the following observations: (1) in the era before antibiotic therapy neurosyphilis was more likely to develop in patients with reactive nontreponemal tests in both spinal fluid and blood than in patients with nonreactive CSF studies[11]; (2) with nontreponemal tests approximately 4 percent of patients with neurosyphilis will have reactivity in the spinal fluid despite normal studies in the blood[12] and (3) in late syphilis treponemal tests have significantly greater reactivity than nontreponemal studies.[10] The availability of the very sensitive fluorescent treponemal antibody tests in tertiary syphilis would seem to be a powerful adjunct to the detection of CNS involvement.

However, the role of the CSF-FTA test and its many modifications in the evaluation of neurosyphilis remains uncertain.[9,11,13] The unabsorbed FTA test, for example, produced a positive response in 4.5 percent of normal CSF.[14] Dilution of specimens and addition of sorbent (CSF-FTA-ABS) will decrease the incidence of these false-positive results but at the expense of sensitivity.[15] To date no standard approach has been agreed upon. The lack of productivity in the CSF-FTA-ABS was reinforced by Mahony and co-workers,[13] who noted the tests to be positive in only 75 percent of 20 patients with clinical neurosyphilis. Of concern in regard to the interpretation of the CSF-FTA tests is the question of the source of the detected antibody. The finding of a direct correlation between CSF reactivity and higher blood titers[11,16] suggests that the immunoglobulins responsible for the production of the CSF-FTA tests may enter the spinal fluid by diffusion from the blood. This finding has been confirmed in the French literature.[17] The meaning of a positive CSF-FTA test in the absence of other evidence of CNS disease, then, remains uncertain because it may merely represent diffusion of the antibody into the CSF from blood. There is apparent agreement in the literature, however, on an important related point: essentially every patient with a positive CSF-FTA-ABS test will have a positive FTA-ABS reaction in the blood. Therefore, a normal serum FTA-ABS test makes testing of the CSF completely unnecessary.[3,11]

False-Positive Tests

False-positive nontreponemal tests for syphilis are well categorized. Such patients have a positive nontreponemal test and a negative FTA or TPI response and are said to be biologic false-positive reactors. These patients can be divided into two groups, those with transient and those with so-called chronic biologic false-positive reactions (Tables 5 and 6). Transient false-positive reactions are most often associated with acute infections or pregnancy.[18] The large number of cases with unclear causes underline the necessity for several determinations before positivity is assumed to result from syphilis. Chronic false-positive reactive reactions occur mainly in patients with autoimmune disease, especially systemic lupus erythematosus (LE) but also with more benign

abnormalities such as rheumatoid arthritis. Leprosy, heroin addiction and old age are commonly listed causes but are rare in a given population; unknown causes unfortunately continue to lead the list.[17] The association of a chronic false-positive serological response with autoimmune disease is substantiated by the finding of associated serological abnormalities, such as antinuclear antibody, rheumatoid factor, LE cells and hypergammaglobulinemia.[10,18] The quantitative VDRL may assist in the identification of false-positive reactors because such cases usually produce titers of less than 1:8.[10,19]

The issue of false-positive FTA-ABS tests is a more difficult one because this test is specific for treponemal antibodies. Cases of false-positive FTA-ABS responses have been clearly documented, however. One subgroup is the borderline positive FTA-ABS test, which has been reported to occur in 2 percent of celibate nuns[20] and in 8.6 percent of general hospital admissions.[21] Nearly half of such patients will have a normal study on follow-up examination and another half will continue to have chronically borderline positivity, the meaning of which is uncertain. In only a small portion of these patients will clearly positive tests subsequently occur. Strongly reactive FTA-ABS findings that appear to be falsely positive have also been reported in occasional patients. Such patients fall into the categories listed above for false-positive nontreponemal tests. The best documented cases have been associated with abnormal serum globulins (such as in rheumatoid arthritis, autoimmune hemolytic anemia and alcoholic cirrhosis) and pregnancy.[10,16]

TABLE 5.—*Acute Biological False-Positive Reactions**†

Cause	*Number of False-Positive Reactions*
Undetermined	24
Recent smallpox vaccination	11
Recent inoculation	5
Infective hepatitis	5
Infectious mononucleosis	3
Viral pneumonia	3
Chicken pox	2
Measles	2
Viral encephalitis	1
Pregnancy	18
TOTAL	74

*To serological test for syphilis.
†Adapted from Catterall.[18]

TABLE 6.—*Chronic Biological False-Positive Reactions**

Cause	*Number*
Undetermined	74
Systemic lupus erythematosus	10
Rheumatoid arthritis	6
Rheumatic heart disease	6
Possible connective tissue disease	6
Probable multiple sclerosis	6
Discoid lupus erythematosus	4
Hepatic cirrhosis	2
Hemolytic anemia	2
Polyarteritis nodosa	2
Hashimoto thyroiditis	2
Sjögren syndrome	2
Psychotic illness	2
Chronic nephritis	2
Heroin addiction	2
Peripheral vascular disease	2
Systemic sclerosis	1
TOTAL	130

*Adapted from Catterall.[18]

Antibiotic Therapy

The identification of *T pallidum* in multiple body organs (lymph nodes, aqueous humor, CSF, brain, arteries, bone) following full treatment for syphilis has caused much interest in the past decade.[22] This occurrence has been reported most frequently in aqueous humor.[23] The subsequent documentation that many of the alleged organisms were artifacts of glass filament makes this mass of data suspect.[24] More recently, *T pallidum* has been recovered from the spinal fluid of two patients given adequate therapy for neurosyphilis and in whom all CSF determinations had returned to normal.[25] The importance of such findings is a matter of debate.[22] These issues have led to a reevaluation of the adequacy of standard treatment regimens for tertiary syphilis by the measurement of penicillin levels in CSF and a comparison of these results with known spirocheticidal concentrations. The recommended treatment schedules for tertiary syphilis include aqueous procaine penicillin G, 600,000 units per day intramuscularly for 15 days, crystalline penicillin G, 2 to 4 million units intravenously every four hours for ten days and benzathine penicillin G, 2.4 million units intramuscularly per week for three weeks.[26,27] Mohr[28] noted that two patients treated with aqueous penicillin G, 5.0 and 10.0 million units per day had spinal fluid penicillin levels of 0.3 to 2.4 μg per ml, respectively (spirocheticidal levels being greater than 0.3 μg per ml). However, 12 of 13 patients treated with benzathine penicil-

lin G had no detectable penicillin in the CSF. Thus, benzathine penicillin G may be inadequate treatment for CNS syphilis.

Summary

Neurosyphilis has become infrequently diagnosed in recent years, possibly as the result of routine antibiotic treatment of nontreponemal disease. Diagnostic difficulty may be the result of neurosyphilis presenting as a *forme fruste* of classic neurosyphilis (tabes dorsalis, general paresis and meningovascular syphilis) or as an unrecognized but typical form of this now unfamiliar disease. Therefore, increased reliance is placed on serological tests. Because the nontreponemal tests (such as VDRL) may be negative in as many as 30 percent of cases of neurosyphilis, specific treponemal tests (such as FTA-ABS) are required for accurate detection. The role of the FTA test in the evaluation of spinal fluid samples remains uncertain, but a negative serum FTA-ABS response excludes positive serological findings in the CSF. The standard therapy of benzathine penicillin G, 2.4 million units per week for three weeks, may be inadequate treatment for neurosyphilis.

REFERENCES

1. Hooshmand H, Escobar MR, Kopf SW: Neurosyphilis. JAMA 291:726-729, Feb 1972

2. Joyce-Clarke N, Molteno ACB: Modified neurosyphilis in the Cape Peninsula. S Afr Med J 53:10-14, Jan 1978

3. Modified neurosyphilis (Editorial). Br Med J 3:647-648, Sep 1978

4. Syphilis, a Synopsis, Public Health Service Publication No. 1660. 1968, US Dept of Health, Education, and Welfare

5. Merritt HH: A Textbook of Neurology. Philadelphia, Lea & Febiger, 1973

6. Kurtzke JR: Epidemiology of myasthenia gravis, *In* Schoenberg BS (Ed): Neurological Epidemiology, Adv Neurol 19:545-564, 1978

7. Catterall RD: Neurosyphilis. Br J Hosp Med, Jun 1977 pp 585-604

8. Luxon L, Lees AJ, Greenwood RJ: Neurosyphilis today. Lancet 1:90-93, Jan 1979

9. Jaffee HW: The laboratory diagnosis of syphilis. Ann Intern Med 83:846-849, Dec 1975

10. Sparling PF: Diagnosis and treatment of syphilis. N Engl J Med 284:642-653, Mar 1971

11. Jaffee HW, Larsen SA, Peters M, et al: Tests for treponemal antibody in CSF. Arch Intern Med 138:252-255, Feb 1978

12. Dewhurst K: Atypical serology in neurosyphilis. J Neurol Neurosurg Psychiat 31:496-500, Oct 1968

13. Mahony JDH, Harris JRW, McCann JS, et al: Evaluation of the CSF-FTA-ABS test in latent and tertiary treated syphilis. Acta Derm Venereol (Stockh) 52:71-74, 1972

14. Escobar MR, Dalton HP, Allison MJ: Fluorescent antibody tests for syphilis using cerebrospinal fluid. Am J Clin Path 53:886-890, Jun 1970

15. Wilkinson AE: Fluorescent treponemal antibody tests on cerebrospinal fluid. Br J Venereal Dis 49:346-349, Aug 1973

16. Traviesa DC, Prystowsky SD, Nelson BJ, et al: Cerebrospinal fluid findings in asymptomatic patients with reactive serum fluorescent treponemal antibody absorption tests. Ann Neurol 4: 524-530, Dec 1978

17. Ripault J, Colombani J: Le test d'immuno-fluorescence appliqué au diagnostic de la syphilis. Comparaison avec le test de Nelson et la sérologic classique. II Etude de 411 liquides cephalorachidiens. Path Biol (Paris) 12:276-285, Mar 1964

18. Catterall RD: Systemic disease and the biological false positive reaction. Br J Venereal Dis 48:1-12, Feb 1972

19. Tuffanelli DL, Wuepper KD, Bradford LL, et al: Fluorescent treponemal-antibody absorption tests. N Engl J Med 276: 258-262, Feb 1967

20. Goldman JN, Lantz MA: FTA-ABS and VDRL slide test reactivity in a population of nuns. JAMA 217:53-55, Jul 1971

21. Cohen P, Stout G, Ende N: Serologic reactivity in consecutive patients admitted to a general hospital. Arch Intern Med 124:364-367, Sep 1969

22. Dunlop EMC: Persistence of treponemes after treatment. Br Med J 2:577-580, Jun 1972

23. Smith JL, Israel CW: Treponemes in aqueous humor in late seronegative syphilis. Trans Amer Acad Ophthal Otolargyngol 72:63-75, Jan-Feb 1968

24. Montenegro ENR, Nicol WG, Smith JL: Treponema-like forms and artifacts. Am J Ophthal 68:197-205, Aug 1969

25. Tramont EC: Persistence of *Treponema pallidum* following penicillin G. therapy. JAMA 236:2206-2207, Nov 1976

26. Syphilis: Recommended treatment schedules, 1976, Center for Disease Control. Ann Intern Med 85:94-96, Jul 1976

27. Syphilis: Recommended treatment schedules. Medical Letter 19:105, Dec 1977

28. Mohr JA: Neurosyphilis and penicillin levels in cerebrospinal fluid. JAMA 236:2208-2209, Nov 1976

BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

MGH TEXTBOOK OF EMERGENCY MEDICINE—Emergency Care as Practiced at the Massachusetts General Hospital—Editor: Earle W. Wilkins, Jr, MD, Associate Professor of Surgery, Harvard Medical School; Chief of Emergency Services and Visiting Surgeon, Massachusetts General Hospital; Associate Editors; James J. Dineen, MD, Assistant Professor of Medicine, Harvard Medical School; Associate Physician, Massachusetts General Hospital; and Ashby C. Moncure, MD, Assistant Clinical Professor of Surgery, Harvard Medical School; Associate Visiting Surgeon, Massachusetts General Hospital. The Williams & Wilkins Company, 428 E. Preston Street, Baltimore, MD (21202), 1978. 804 pages, with 308 illustrations, $59.95.

Emergency medicine has developed over the past decade reflecting sophisticated technologic achievements in American medicine and the public's awareness of these advances. The growth in this field also reflects changing patterns of medical practice with an emphasis on increasing specialization and less availability of around-the-clock medical services from physicians in practice. Funding of emergency medical services systems by the federal government has contributed a new area of responsibility to this developing area of medicine. Training programs, including both residencies and fellowships, are now available to those who wish to make emergency medicine their careers.

Although comprehensive reference textbooks in emergency medicine have been published abroad for a number of years, these texts have generally not met the needs of emergency physicians in the United States. Emergency medicine books in this country have largely assumed the form of practical handbooks and of monographs covering certain specific areas of the field, such as medical emergencies. In 1978 two comprehensive American works were published for the first time: *Principles and Practice of Emergency Medicine*, edited by George R. Schwartz and published by W. B. Saunders Company, and the *MGH Textbook of Emergency Medicine*.

Wilkins' textbook of emergency care as practiced at the Massachusetts General Hospital is divided into five sections. Section one covers pathophysiologic principles of life support including cardiopulmonary resuscitation and shock. Sections two and three review medical and surgical emergencies by organ system. Section four illustrates certain areas of emergency ward management and nursing responsibility. Section five is an appendix of invasive techniques commonly used in emergency departments.

The *MGH Textbook* is truly comprehensive but it avoids the pitfalls of attempting to be an in-depth reference work for each of the specialties which together constitute emergency medicine. Rather, the book concentrates on diagnosis and management of patients in the initial phase of care. The text is compact, the volume is easy to hold and the index is complete, making this an ideal reference work for use on emergency wards.

Since patients often arrive at the emergency department with symptoms and signs rather than diagnoses, a major section of the book should have been devoted to differential diagnoses of several common presenting problems (such as dyspnea or coma). More space also should have been alloted to special problems sometimes encountered by emergency physicians, such as bites and stings, radiation injury and near drowning. Given the prevalence of patients with dermatologic problems in an emergency department, a more comprehensive chapter of common dermatoses should have been included.

Management skills are neglected in most medical schools and even in many emergency medicine residencies; emergency physicians, however, often are responsible for managing departments with large budgets and numerous personnel. Unfortunately the section on administration in this text merely describes emergency management as it exists at Massachusetts General Hospital and does not attempt to teach some of the necessary skills. Financial aspects of an emergency department are not considered. Costs associated with increasing use of the emergency ward contribute to the escalating cost of health care in this country and this text might have pioneered in this area by addressing the issues of cost effectiveness and cost control.

The *MGH Textbook of Emergency Medicine* is well written and clinically sound. In conjunction with other comprehensive reference texts in the specialities, it will serve as a useful addition to the libraries of emergency physicians and physicians in specialties where patients with acute illnesses are frequently encountered.

JOHN E. CONTE, JR, MD
Associate Professor of Medicine
Chief, Division of Emergency Medicine
WILLIAM F. OWEN, JR, MD
Coordinator of Emergency Medicine Education
Division of Emergency Medicine
University of California, San Francisco

* * *

RESPIRATORY FUNCTION OF THE LUNG AND ITS CONTROL—Fred S. Grodins, MD, PhD, Professor and Chairman, Department of Biomedical Engineering, and Professor of Physiology; and Stanley M. Yamashiro, PhD, Associate Professor of Biomedical Engineering, University of Southern California, Los Angeles—in the series: MODERN CONCEPTS IN MEDICAL PHYSIOLOGY—Lysle H. Peterson, MD, Consulting Editor. Macmillan Publishing Co., Inc., 866 Third Avenue, New York City (10022), 1978. 148 pages, $13.50 (cloth), $9.95 (paperback).

Grodins and Yamashiro have undertaken an awesome task in a relatively short text: to describe the components of respiratory function of the lung *and* their control using a systems analysis approach. The overall behavior of a complex system is examined (largely mathematically and with block diagrams) in terms of "interacting unit processes." An introductory chapter describes the lung as a metabolic servomechanism designed to match gas exchange rates in lung and periphery while maintaining internal chemical concentrations of arterial oxygen, carbon dioxide and hydrogen ion constant. After a chapter on gas laws the authors use subsequent chapters to describe six "unit processes" of pulmonary ventilation, pulmonary diffusion, blood chemical processing, circulation tissue diffusion and tissue metabolism, finally incorporating the concept of negative feedback as a major factor in controlling respiratory function.

The chapter on gas laws contains an error in one formula, describes body plethysmography in a single paragraph, and assumes an elementary knowledge of calculus. The problem set is helpful.

A chapter on the ventilatory apparatus describes lung volumes, flow rates, elastic and resistive properties (including Poiseiulles law and the Reynolds number),

respiratory work, surface tension, frequency dependence of resistance and compliance, the flow volume curve, and closing volume. Three "electrical analogs" of the ventilatory apparatus are diagrammed that may elucidate concepts for those familiar with electrical circuitry. Chapters on the pulmonary gas exchanger, tissue gas exchange, and blood buffers and acid base balance also describe many important concepts mathematically.

The final chapter, control of pulmonary ventilation, describes how alveolar ventilation is affected by levels of arterial oxygen, carbon dioxide, and pH emphasizing the servomechanism concept.

The authors do succeed in analyzing respiratory function of the lung and its control using the systems analysis approach although discussion of the unit processes are brief. The historical development of important physiological concepts are well referenced at the end of each chapter.

Because of the brief and largely analytical development of many concepts this book will be of most use to those already familiar to some degree with pulmonary physiology and to those who understand concepts mathematically without extensive written elaboration. This text will be of less interest to an average medical student or practicing physician than to a biomedical engineer or specialist in a pulmonary related field.

GIBBE H. PARSONS, MD
Assistant Professor of Medicine
Pulmonary Section
University of California, Davis
School of Medicine
Davis, California

* * *

TEXTBOOK OF GERIATRIC MEDICINE AND GERONTOLOGY—Second Edition—Edited by J. C. Brocklehurst, MD, MSc, FRCP (Glas and Ed), Professor of Geriatric Medicine, University of Manchester. Churchill Livingstone—Medical Division of Longman Inc., 19 West 44th St., New York City (10036), 1978. 838 pages. $65.00.

It is extraordinarily difficult to revise the standard work in any field. Since it appeared in 1973, Professor Brocklehurst's book has been a mainstay of geriatric teaching in England. It now reappears after five years with additional chapters, including important sections on cerebral effects of drugs and on geriatric anesthesia, and with rewritten sections on biological gerontology, thyroid disease, stroke and social roles of the elderly. In a field such as the biology of aging, every textbook goes to press with the certainty of omissions in such a rapidly developing subject—the biological and theoretical reviews here give excellent summaries of the single-process models of aging in vogue around 1976, but just missed the appearance of a vogue for software theories based on the hypothalamic lifespan clock. This is of little importance to clinicians, however, because what they will derive from a book such as this is the general flavor of fundamental age research. The major concerns are excellently covered, system by system. The main areas of geriatric special knowledge—differences in presentation from textbook "adult" patterns, nonspecific presentation of specific disease, avoidance of iatrogenic mischief with common drugs, and above all the essential social concerns for decent geriatric medicine ranging from the abandonment of the folklore of decrepitude to the provision of day-centers and in-home services—are dealt with in detail. Special problems, particularly the management of incontinence, on which Brocklehurst himself has done pioneer work, are also first class. The weakest section—that on psychiatry—should be revised for the next edition to cover a more systematic account of "senile" dementias and an introduction to nonthreatening mental testing: the present chapter, from the 1973 edition, does not clearly distinguish multiembolic from Alzheimer type dementias (and, incidentally, contains the statement that "the vast majority of males" have become impotent by age 75, which is not borne out by studies). Part of this deficiency is made up in other chapters on neurology and on experimental drugs.

In spite of some valiant efforts in various centers, geriatrics in America still presents a yawning gap in most student and postgraduate training. There has been no American book of equal scope since Cowdry, and there is still none of comparable quality. Neither of the two most used textbooks of medicine refer to geriatric medicine. In view of the demographics of modern practice, Brocklehurst's book, together with Hodkinson's *Common Symptoms of Disease in the Elderly*, ought to be obligatory prelicensure reading for students both until and after they are finally exposed to dedicated geriatricians as teachers, and should be on the shelves of every practitioner, regardless of specialty, who does not confine his ministrations to babies.

ALEX COMFORT, MD
Consultant, Geriatric Psychiatry
Brentwood VA Medical Center
Los Angeles

* * *

THYROID CANCER—Editor: Larry D. Greenfield, MD, Director, Department of Nuclear Medicine; Co-Director, Thyroid Oncology Service; Radiation Oncologist, City of Hope National Medical Center, Duarte, California. CRC Press, Inc., 2255 Palm Beach Lakes Blvd., West Palm Beach, FL (33409), 1978. 267 pages, $64.95, outside U.S. $74.95.

Thyroid cancer is not a common disease and may be underestimated because of its indolent growth, or overwhelming in the rare but rapidly fatal illness. Dr. Greenfield has produced a small but comprehensive and authoritative book on thyroid cancer which will be very helpful to those clinicians who manage such patients. He has assembled an excellent group of specialists who review in succinct chapters the salient features. Thus, there are chapters on embryology, pathophysiology and diagnostic techniques, and separate discussions of the management of the various forms of the disease. Many new aspects are emphasized: for example, the differences in the development of the parafollicular cells (calcitonin secreting) from thyroid cells (thyroglobulin secreting) as noted on electron microscopy. There is an excellent review of the problem of radiation-induced thyroid cancer, by Drs. Hempleman and Furth. Sections on management of thyroid cancer are clinically oriented and very helpful. The indication for and results of radiation therapy and chemotherapy are carefully reviewed and these modalities are put into proper perspective.

As in any text with multiple authors there is some overlap; for example, the use of thyroglobulin and calcitonin as markers for differentiated thyroid cancer is mentioned in several chapters. The excellent photomicrographs of thyroid pathology by Dr. LiVolsi would have been much more effective in color. But generally, this is a fine book, authoritative and informative, short and well written. It has a good index and each chapter has an excellent and current bibliography. It will be of great value to endocrinologists, internists and surgeons, and others interested in the present status of the diagnosis and management of thyroid cancer.

FRANCIS S. GREENSPAN, MD
Clinical Professor of Medicine and Radiology, and
Chief, Thyroid Clinic
University of California
San Francisco

THE METABOLIC MANAGEMENT OF THE CRITICALLY ILL—Douglas W. Wilmore, MD, U.S. Army Institute of Surgical Research, Brooke Army Medical Center, Fort Sam Houston, Texas—Reviewing Surgical Topics Series Edited by Thomas King, MD and Keith Reemisma, MD, Columbia University College of Physicians and Surgeons, New York. Plenum Publishing Corporation, 227 West 17th St., New York City (10011), 1977. 260 pages, $22.50.

One of the major deficiencies in the medical education of physicians is the area of nutrition. As Dr. Wilmore points out, nutritional surveys carried out on medical and surgical services in large hospitals demonstrate evidence of protein-calorie malnutrition in over 25 percent of patients on those services. Thus, any monograph on the subject of the metabolic and nutritional care of patients in hospital that is informative, easy to read and directly applicable to patient care is welcome.

Dr. Wilmore has synthesized a great quantity of information, and has drawn on his own extensive experience with patients suffering from thermal burns, to produce an easy-to-read book. The book contains five chapters dealing with energy and energy balance, the control of body temperature, hormonal control of body fuels, alterations that take place in intermediary metabolism during illness, and the nutritional management of seriously ill patients. Each chapter is divided into subsections which are headed by questions (such as "What is RQ? Why is it useful?"), followed by a relatively succinct answer to the questions. A pad of metabolic and nutritional worksheets is provided and the appendix to the book describes in detail how the worksheets should be used in order to calculate the nutritional requirements of the patient. The majority of the essential and practical information is contained in the first and last chapters and the appendix. The middle three chapters provide an up-to-date summary of the biochemical problems that affect energy metabolism during illness.

The author has appropriately reproduced numerous useful nomograms for calculating the nutritional requirements in the appendix section and has provided a loose-leaf copy of the appendix that could be posted on patient wards or in an intensive care unit.

The major problem with this monograph is the frequent use of the question-oriented subheadings in each chapter. This tends to decrease the overall adhesiveness of the individual topics covered. The book does provide a useful overview and is heavily annotated and, therefore, will be of use as a primer to senior medical students, medical and surgical house officers, and physicians who deal with large numbers of patients with acute critical illness or chronic disorders. Utilization of Dr. Wilmore's nutritional and metabolic support plan should certainly reduce the incidence of hospital malnutrition.

GLENN D. BRAUNSTEIN, MD
Director, Endocrinology
Cedars-Sinai Medical Center
Associate Professor of Medicine
UCLA School of Medicine
Los Angeles

* * *

ANTIMICROBIAL PRESCRIBING—Harold C. Neu, MD, Professor of Medicine and Pharmacology, Columbia University; Head, Division of Infectious Diseases, Columbia-Presbyterian Medical Center, New York. Antimicrobial Prescribing, Inc., P.O. Box 3153, Princeton, NJ (08540), 1979. 111 pages, $19.95.

This is one of several recently available handbooks dealing with the appropriate selection and use of antimicrobial agents. The book can be roughly divided into four parts. The first deals with the selection of agents for specific infections and/or microbial pathogens. The second discusses the spectrum and pharmacology of the most commonly used chemotherapeutics, while the third deals with a variety of other treatment problems. These include drug interactions and toxicity, prophylaxis and dosage adjustment during renal failure. Finally, a brief section on vaccines and immunizations is included.

This material is presented almost entirely in tabular form, allowing the author to organize an enormous amount of data into relatively little space. The format of the tables is simple and the data are easy to peruse. The sections dealing with specific clinical infections, antimicrobial drug interactions and prophylaxis are particularly good.

The author's quest for brevity, however, has led to several irritating flaws. Abbreviations such as PRP (penicillinase resistant-penicillins) and oral flora (anaerobic oral flora) are used without adequate footnoting, and comments are often so foreshortened that the reader is left confused or uncertain of the author's message. Moreover, vital information such as the importance of maintaining an airway in acute epiglottitis is absent. The author several times mentions anaerobic streptococci—presumably a reference to peptostreptococci—thus perpetuating a common but unfortunate mistake. Dosing information, such as that for metronidazole in the treatment of *Trichomonas vaginalis* infections, is occasionally in error as well. Finally, it is sometimes difficult to find specific antibiotic doses for certain clinical problems. For instance, in the section dealing with infections of the central nervous system, methicillin and chloramphenicol are recommended for *S aureus* meningitis. Turning to the section dealing with the penicillins one finds the dose for methicillin listed as 1 to 2 grams every four to six hours. Examining the next logical table, "Antibiotic Dosage by Condition," is of no help since methicillin is not listed under meningitis. It is only after turning to a fourth table, "Dosage of Antibiotics in the Treatment of Life-Threatening Infections in Adults and Older Children," that the appropriate dosing information is found.

Considering the clarity of format and the enormous amount of data presented, such flaws are relatively minor. Nevertheless, they are disconcerting in a publication selling for nearly 20 dollars. It is hard to recommend this book to a practicing physician when comparable or nearly comparable publications are available at much lower cost.

JAMES J. PLORDE, MD
Professor of Medicine and Laboratory Medicine
University of Washington
Seattle

* * *

DRUG INTERACTIONS—Clinical Significance of Drug-Drug Interactions and Drug Effects on Clinical Laboratory Results—Fourth Edition—Philip D. Hansten, Pharm D, Associate Professor of Clinical Pharmacy, College of Pharmacy, Washington State University, Pullman, WA. Lea & Febiger, 600 Washington Square, Philadelphia (19106), 1979. 552 pages, $16.00.

The task of keeping abreast of drug-drug and drug-food interactions is difficult considering the large number of drugs available and the frequency with which patients are simultaneously treated with more than one drug. The fourth edition of *Drug Interactions* is a welcome update of the rapidly expanding and changing field of drug-drug interactions. Hansten's clear and concise style, which were hallmarks of previous editions, is maintained in the new edition.

The book contains two parts: Part 1, "Drug-Drug Interventions," contains 16 chapters that represent major groups of drugs (oral anticoagulants, anticonvulsants, and so forth). The clinical importance of the drug interaction is indicated by the three different type faces used: (1) Bold type—major clinical significance, interactions that are well documented or have the potential of being harmful to the patient; (2) Italic—moderate importance,

interactions for which more documentation is needed or the potential for harm is less, (3) Roman—of minor importance. The above format is also used in the index, the key to successful use of the book. The text is further organized in a manner that facilitates quick access to the salient points of interest to the drug-drug interaction: mechanism, clinical significance and management of the patient.

Part II documents the effects of drugs on common clinical laboratory tests carried out on urine, blood, serum or plasma.

A new appendix organizes drugs that have been documented to cause hepatotoxicity and alter hepatic function test results into a convenient table for easy reference.

The book is highly recommended for physicians, pharmacists and other health professionals concerned with drug-drug interactions.

LARRY A. WHEELER, PhD
Research Pharmacologist
Wadsworth VA Hospital
Los Angeles

* * *

COMPUTERS FOR THE PHYSICIAN'S OFFICE—Volume II in the MEDICAL COMPUTING Series—Joan Zimmerman, D Phil, Biomedical Computer Laboratory, Washington University, St. Louis, Alan Rector, MD, Health Services Research Group, University of Nottingham. Research Studies Press, P.O. Box 92, Forest Grove, OR (97116), 1978. 302 pages, $21.50.

This book, the joint effort of a computer specialist experienced in medical applications, and a physician-user of computers in medical records management, helps meet the need for timely reviews of this field. The authors deliver much more than the title promises, and they review medical computing carried out in a variety of settings and for a number of different purposes. Their coverage of existing medical information systems, particularly in the United States and United Kingdom, appears reasonably complete, and the bibliography and other appended materials should prove useful to present workers in the field, as well as to newcomers.

The book is long on fact, and short on theory—a fault shared by much of the literature of this field—and it is both a catalogue of hardware, software and systems, and an index to the reports of their employment. As a key to the literature of current medical computing systems, and the data processing aspects of such activities as medical audit and the administrative uses of the medical record, the book is highly recommended. Its detailed discussion of ambulatory care records should make it of interest to its designated audience.

Whether the book is apt to provide answers to the kinds of questions that may come to mind when a physician thinks about having a computer in his office, is something else. It seems to be generally agreed that physicians require a fair amount of information during a day's work, and it is obvious that a variety of resources, formal or informal, costly or inexpensive, are available for this purpose. It is also beyond dispute that computers can do things to and with information. When we attempt to say much more than this, these bodies of agreement begin to crumble. The subject to which conversation then quickly turns, and which is the primary topic of this book, is how nice it would be if we could put the medical record in a computer. With this attention shift, preoccupation with the medical record becomes an end in itself. This end is perhaps pursued less intensively by a physician, than by those peering over his shoulder and studying, measuring or regulating what he or she is doing.

But a physician in his office, wondering whether a computer terminal will fit on that table in the corner, is unaware of this fixation of our field. If asked what his information needs are, he might respond that it would be nice if he could dial up a computer and ask some questions: whether or not a patient allergic to alphamycin might tolerate betamycin, or what is the most recent review article on the treatment of herpes simplex, or even whether the computer at the other end of line might be able to suggest a differential diagnosis for a patient with nosebleed and pruritus. If these types of question were what he sought, he would not find answers in this book. The index does not include anything on MEDLARS or information retrieval, or diagnosis, although several of the automated consultant projects are mentioned. Other topics are discussed in more detail. For example, cost-benefit analysis is distinguished from cost-effectiveness analysis in that under the former procedure a benefit is "the increase in expected life and quality of life" (which the authors grant is difficult to measure), while under the latter the benefit is expressed "in such terms as lives saved or years made more comfortable." With this difference clearly in mind, one is then able to produce "explicit statements about the beliefs and values upon which are based allocation decisions." Meanwhile, a physician in his office will probably continue to use the *PDR*, read the throwaway literature and consult with his colleagues.

The advent and recent rapid growth of microprocessor technology, alluded to briefly in the book, has raised high hopes as a means for providing a low-cost, office-based computing resource. A number of physicians, motivated by the hobby aspect of personal computing, are developing systems of one kind or another for their own office use. This grass roots activity cannot but help in the maturing of the field of medical computing. But for the computer to find its natural and proper roles in medical practice, information systems must offer much more than merely being affordable. They must become more tolerant of human users (and misusers). They must come to grips—much more than at present—with the fact that computers are intrinsically more suited to *hard* science calculations, than to processing clinical information with its incompleteness, and its *maybe* and *perhaps*. I do not mean to imply that there are not more computers in our future, and indeed in our offices. Before the latter happens, however, there are many questions to be answered regarding the nature, use, authenticity and timeliness of medical information. These questions are not addressed by the authors. However, the experience gained with institutional systems of the type the authors describe will help provide the deeper understanding needed before office computers achieve the reality they surely have in store.

As indicated at the beginning, the authors deliver more than they promise; given their obvious hard work, it is regrettable that the publishers deliver so little. The review copy fell halfway out of its binding—the front end-papers having split—before I completed the preface and foreword. The copy in our library I found, too, to have fared poorly with ordinary use.

MARSDEN S. BLOIS, MD, PhD
Professor of Medical Information Science
University of California, San Francisco
San Francisco

in memoriam

California Medical Association

ALLEN, ORAH KNAPP, San Francisco. Died November 22, 1980 in Los Altos, aged 102. Graduate of California Eclectic Medical College, Los Angeles, 1915. Licensed in California in 1915. Dr. Allen was a retired member of the San Francisco Medical Society.

BERGER, ADOLPHUS A., San Francisco. Died November 8, 1980, aged 81. Graduate of Washington University School of Medicine, St. Louis, 1925. Licensed in California in 1926. Dr. Berger was a retired member of the San Francisco Medical Society.

BURKS, ARTHUR LYNN, San Francisco. Died October 30, 1980 in San Francisco, aged 64. Graduate of the University of Oklahoma School of Medicine, Oklahoma City, 1939. Licensed in California in 1940. Dr. Burks was a member of the San Francisco Medical Society.

CLOYD, DAVID HAMPTON, Escondido. Died November 1, 1980 in Escondido of cancer, aged 50. Graduate of the University of Nebraska College of Medicine, Omaha, 1955. Licensed in California in 1963. Dr. Cloyd was a member of the San Diego County Medical Society.

DORMAN, GEORGE E., Palm Desert. Died September 9, 1980, aged 72. Graduate of the University of Maryland School of Medicine, Baltimore, 1934. Licensed in California in 1967. Dr. Dorman was a member of the Riverside County Medical Association.

FEIST, JOHN P., San Francisco. Died November 8, 1980, aged 70. Graduate of Kansas City College of Osteopathy and Surgery, Kansas City, MO, 1952. Licensed in California in 1953. MD degree from California College of Medicine, 1962. Dr. Feist was a member of the San Francisco Medical Society.

GIBBS, WILLIAM M., San Marcos. Died September 28, 1980 in Escondido of lung cancer, aged 88. Graduate of Northwestern University Medical School, Chicago, 1930. Licensed in California in 1930. Dr. Gibbs was a member of the Los Angeles County Medical Association.

KWAN, SUNG TAO, Berkeley. Died November 8, 1980 in Hayward, aged 84. Graduate of Rush Medical College, Chicago, 1924. Licensed in California in 1950. Dr. Kwan was a member of the San Francisco Medical Society.

MOORE, LA RUE, San Francisco. Died October 29, 1980, aged 79. Graduate of the University of Oklahoma School of Medicine, Oklahoma City, 1923. Licensed in California in 1923. Dr. Moore was a member of the San Francisco Medical Society.

MOTT, JOHN M., Sacramento. Died November 11, 1980 in Orangevale of heart disease, aged 64. Graduate of the Stanford University School of Medicine, Palo Alto-San Francisco, 1943. Licensed in California in 1943. Dr. Mott was a member of the Sacramento-El Dorado Medical Society.

NELSON, DONALD R., San Francisco. Died October 26, 1980 in Petaluma, aged 77. Graduate of the University of Cincinnati College of Medicine, 1933. Licensed in California in 1945. Dr. Nelson was a retired member of the San Francisco Medical Society.

PAPADOPOULOS, GEORGE, Fresno. Died October 23, 1980, aged 56. Graduate of the National University of Athens School of Medicine, 1951. Licensed in California in 1961. Dr. Papadopoulous was a member of the Fresno-Madera Medical Society.

PERKINS, WILLIAM A., Oakland. Died November 10, 1980, aged 91. Graduate of Harvard Medical School, Boston, 1916. Licensed in California in 1919. Dr. Perkins was a retired member of the Alameda-Contra Costa Medical Association.

STEIN, DAVID HERBERT, Oakdale. Died August 21, 1980 in Oakdale of metastatic carcinoma, aged 56. Graduate of the University of Toronto Faculty of Medicine, 1947. Licensed in California in 1973. Dr. Stein was a member of the Stanislaus Medical Society.

WILSON, DAVID COLE, Charlottesville, Virginia. Died October 30, 1980 in Charlottesville, aged 88. Graduate of the University of Virginia School of Medicine, Charlottesville, 1919. Licensed in California in 1960. Dr. Wilson was a retired member of the Napa County Medical Society.

Washington State Medical Association

CLARKE, DONALD E., Longview. Died October 9, 1980, aged 75. Graduate of the University of Minnesota Medical School, Minncapolis, 1932. Licensed in Washington in 1932. Dr. Clarke was a member of the Cowlitz-Wahkiakum Medical Society.

FREEMAN, GEORGE W., Seattle. Died September 20, 1980, aged 79. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1928. Licensed in Washington in 1929. Dr. Freeman was a member of the King County Medical Society.

PETERSON, EVERETT R., Everett. Died October 18, 1980, aged 65. Graduate of the University of Illinois College of Medicine, Chicago, 1943. Licensed in Washington in 1947. Dr. Peterson was a member of the Snohomish County Medical Society.

WOOLERY, JAMES W., Vancouver. Died October 11, 1980, aged 63. Graduate of the University of Oregon Medical School, Portland, 1943. Licensed in Washington in 1944. Dr. Woolery was a member of the Clark County Medical Society.

Is there a generic equivalent for drug research?

Estimated Drug Industry Investment in R&D*

Frankly, the dollars say no.

By the most generous estimates, generic manufacturers contribute barely 3% of the more than one billion dollars spent annually in the laboratories of American drug firms on research and development of new drugs.

For the last quarter of a century, virtually all of the major new drugs that imitators imitate have originated with a handful of research-oriented firms well known to all.

While our national investment in research has been declining steadily for a decade, the American pharmaceutical industry has actually been increasing its commitment, so that it now spends over five times the national average. No other industry dedicates a higher percentage of its profits to research. No industry in America depends less on government subsidies.

In the last two decades, the cost of introducing a significant new drug has risen from roughly $4,000,000 to over $50,000,000, while its effective patent life has eroded from seventeen years to less than ten.

Today, the entire research and development commitment of ALL generic manufacturers combined is not enough to develop one single new drug entity.

When you prescribe generics, you switch profits from the innovators to the imitators...and R&D rarely appears on the imitators' budget sheets. Meanwhile, there are *real* people who may have to suffer and perhaps die needlessly if the incentives to progress are removed. It would be sad to abandon our commitment to the future in the short-sighted search for a bargain.

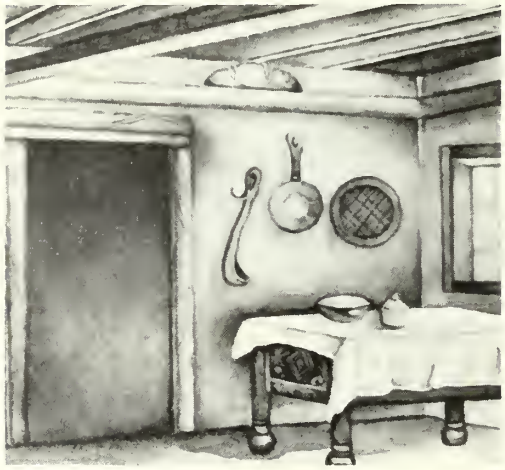
*Based on 1977 published figures available from National Science Foundation and/or Pharmaceutical Manufacturers Association

ROCHE®

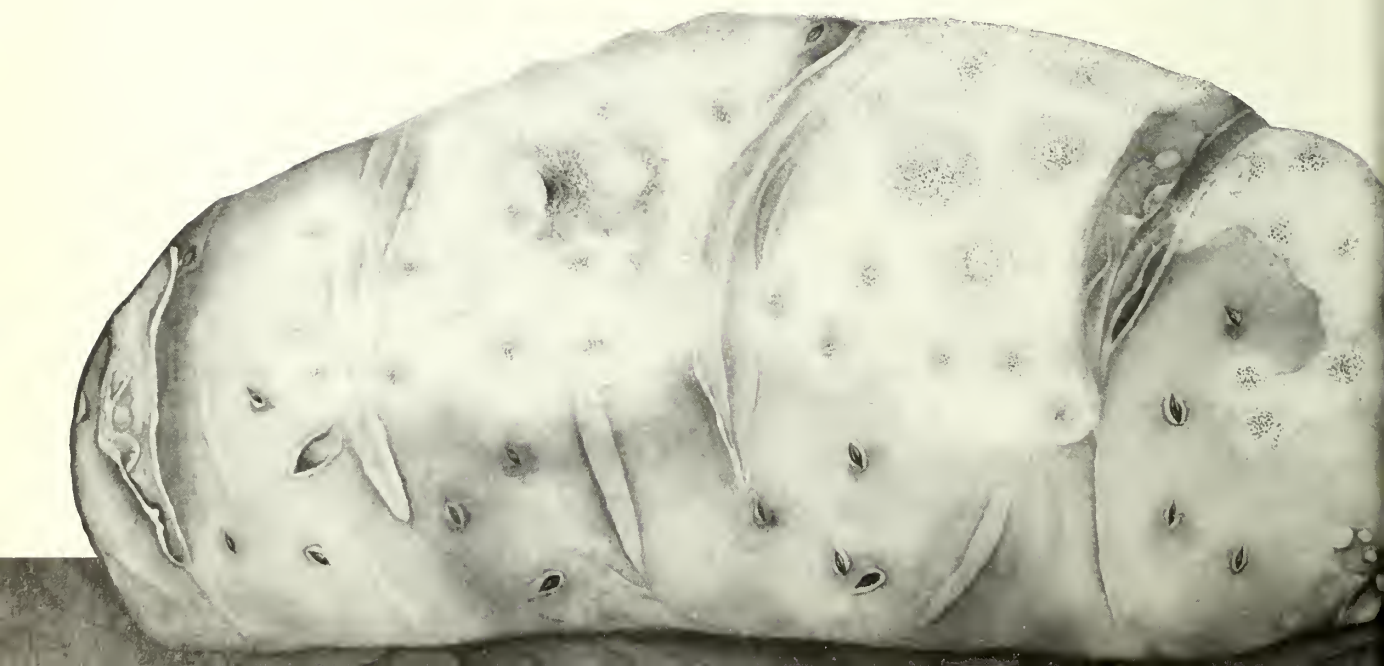
Without the innovators, there could be no imitators

Yesterday's Folk Remedy:

A rye loaf in the rafters.



Early in this century in Central Europe, almost every farm family kept a loaf of moldy rye bread on one of the kitchen beams. When any family member was cut or bruised, it was an old custom to cut a thin slice from the outside of the loaf, mix it into a paste with water, and apply it to the wound with a bandage. It was believed that no infection would then result from the cut.[1]



Today's Tradition:

Tegopen®

(cloxacillin sodium)

for the treatment* of known or suspected staphylococcal infections such as:

- Acute sinusitis
- Furunculosis and carbuncles
- Impetigo
- Secondarily infected dermatitis
- Cellulitis
- Abscesses
- Infected sebaceous cysts

In serious, deep-seated staph infections, 500 mg q.i.d. dosage is recommended.†

- Tegopen has been reported active against 96% of *Staphylococcus aureus*.[2]
- 80% of *S aureus* has been reported resistant to amoxicillin and ampicillin.‡[2]
- 88% of *S aureus* has been reported resistant to penicillins G and V.‡[2]
- Staph resistance to erythromycin may develop during a course of therapy.[3]

Available as 500-mg and 250-mg capsules and Oral Solution 125 mg/5 ml.

Tegopen® (cloxacillin sodium)
Today's Penicillin for Today's Physician

1. Florey HW, Chain E, Heatley NG, et al: *Antibiotics*. London, Oxford University Press, 1949, p 2.
2. Bac-Data Bacteriologic Report, Professional Market Research. 1978-1979. The clinical significance of *in vitro* data is unknown.
3. Erythromycin prescribing information (in *Physicians' Desk Reference*, ed 34. Oradell, NJ, Medical Economics Co, 1980) states that staph resistance may develop during treatment.

See brief summary of prescribing information on an adjoining page.

Copyright © 1981, Bristol Laboratories

*Note: The choice of Tegopen should take into consideration the fact that it has been shown to be effective only in the treatment of infections caused by pneumococci, Group A beta-hemolytic streptococci, and penicillin G-resistant and penicillin G-sensitive staphylococci. If the bacteriology report later indicates that the infection is due to an organism other than a penicillin G-resistant staphylococcus sensitive to cloxacillin sodium, the physician is advised to continue therapy with a drug other than cloxacillin sodium or any other penicillinase-resistant semisynthetic penicillin.

†In serious, life-threatening infections, oral preparations of the penicillinase-resistant penicillins should not be relied on for initial therapy.

‡Not all isolates may have been tested using both discs.

Tegopen®
(cloxacillin sodium)
Capsules and Oral Solution

Brief Summary of Prescribing Information

For complete information, consult Official Package Circular (12) 9/11/75

INDICATIONS:

Although the principal indication for cloxacillin sodium is in the treatment of infections due to penicillinase-producing staphylococci, it may be used to initiate therapy in such patients in whom a staphylococcal infection is suspected. (See Important Note below.)

Bacteriologic studies to determine the causative organisms and their sensitivity to cloxacillin sodium should be performed.

IMPORTANT NOTE:

When it is judged necessary that treatment be initiated before definitive culture and sensitivity results are known, the choice of cloxacillin sodium should take into consideration the fact that it has been shown to be effective only in the treatment of infections caused by pneumococci, Group A beta-hemolytic streptococci, and penicillin G-resistant and penicillin G-sensitive staphylococci. If the bacteriology report later indicates the infection is due to an organism other than a penicillin G-resistant staphylococcus sensitive to cloxacillin sodium, the physician is advised to continue therapy with a drug other than cloxacillin sodium or any other penicillinase-resistant semi-synthetic penicillin.

Recent studies have reported that the percentage of staphylococcal isolates resistant to penicillin G outside the hospital is increasing, approximating the high percentage of resistant staphylococcal isolates found in the hospital. For this reason, it is recommended that a penicillinase-resistant penicillin be used as initial therapy for any suspected staphylococcal infection until culture and sensitivity results are known.

Cloxacillin sodium is a compound that acts through a mechanism similar to that of methicillin against penicillin G-resistant staphylococci. Strains of staphylococci resistant to methicillin have existed in nature and it is known that the number of these strains reported has been increasing. Such strains of staphylococci have been capable of producing serious disease, in some instances resulting in fatality. Because of this, there is concern that widespread use of the penicillinase-resistant penicillins may result in the appearance of an increasing number of staphylococcal strains which are resistant to these penicillins.

Methicillin-resistant strains are almost always resistant to all other penicillinase-resistant penicillins (cross-resistance with cephalosporin derivatives also occurs frequently). Resistance to any penicillinase-resistant penicillin should be interpreted as evidence of clinical resistance to all, in spite of the fact that minor variations in *in vitro* sensitivity may be encountered when more than one penicillinase-resistant penicillin is tested against the same strain of staphylococcus.

CONTRAINDICATIONS:

A history of a previous hypersensitivity reaction to any of the penicillins is a contraindication.

WARNING:

Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents, e.g., pressor amines, antihistamines, and corticosteroids.

Safety for use in pregnancy has not been established.

PRECAUTIONS:

The possibility of the occurrence of superinfections with mycotic organisms or other pathogens should be kept in mind when using this compound, as with other antibiotics. If superinfection occurs during therapy, appropriate measures should be taken.

As with any potent drug, periodic assessment of organ system function, including renal, hepatic, and hematopoietic, should be made during long-term therapy.

ADVERSE REACTIONS:

Gastrointestinal disturbances, such as nausea, epigastric discomfort, flatulence, and loose stools, have been noted by some patients. Mildly elevated SGOT levels (less than 100 units) have been reported in a few patients for whom pretherapeutic determinations were not made. Skin rashes and allergic symptoms, including wheezing and sneezing, have occasionally been encountered. Eosinophilia, with or without overt allergic manifestations, has been noted in some patients during therapy.

USUAL DOSAGE:

Adults: 250 mg. q 6h.

Children: 50 mg./Kg./day in equally divided doses q 6h. Children weighing more than 20 Kg. should be given the adult dose. Administer on empty stomach for maximum absorption.

N.B. INFECTIONS CAUSED BY GROUP A BETA-HEMOLYTIC STREPTOCOCCI SHOULD BE TREATED FOR AT LEAST 10 DAYS TO HELP PREVENT THE OCCURRENCE OF ACUTE RHEUMATIC FEVER OR ACUTE GLOMERULONEPHRITIS.

SUPPLIED:

Capsules—250 mg. in bottles of 100; 500 mg. in bottles of 100.
Oral Solution—125 mg./5 ml. in 100 ml. and 200 ml. bottles.

BRISTOL®

Bristol Laboratories
Division of Bristol-Myers Company
Syracuse, New York 13201

BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

ADVANCES IN CARDIOLOGY—Volume 27: CURRENT CONCEPTS IN CLINICAL CARDIOLOGY—10th Conference on Cardiovascular Disease in Snowmass-at-Aspen Colorado, January 1979—Editor: John H. K. Vogel, MD, Santa Barbara, California. S. Karger AG, Medical and Scientific Publishers, Arnold-Bocklin-Strasse 25, CH-4011 Basel, Switzerland, 1980. 360 pages, $118.75.

ARCHIVES OF FAMILY PRACTICE—Volume I, 1980—Edited by John P. Geyman, MD, Professor and Chairman, Department of Family Medicine, University of Washington School of Medicine. Appleton-Century-Crofts, 292 Madison Avenue, New York City (10017), 1980. 413 pages, $34.50.

BARRON'S HOW TO PREPARE FOR THE NEW (MCAT) MEDICAL COLLEGE ADMISSION TEST—Third Edition—Hugo R. Seibel, Professor of Anatomy, Director of Electron Microscopy, and Curriculum Coordinator, School of Medicine (Year One), School of Basic Sciences, Medical College of Virginia; and Kenneth E. Guyer, Associate Professor of Biochemistry, School of Medicine, Marshall University. Barron's Educational Series, Inc., 113 Crossways Park Drive, Woodbury, NY (11797), 1980. 288 pages, $6.50 list; $5.20 school.

THE BITTER PILL: Doctors, Patients and Failed Expectations—Martin R. Lipp, MD, in private practice in San Francisco. Harper & Row, Publishers, 10 East 53rd Street, New York City (10022), 1980. 204 pages, $10.95.

BODY WORDS—Kathleen N. Daly. Doubleday & Company, Inc., 245 Park Ave., New York City (10017), 1980. 146 pages, $10.95.

BRAIN ALLERGIES: The Psycho-Nutrient Connection—William H. Philpott, MD, and Dwight K. Kalita, PhD, Keats Publishing, Inc., P.O. Box 876, New Canaan, CT (96840), 1980. 229 pages, $15.00.

BURN-OUT: The High Cost of High Achievement—Herbert J. Freudenberger, PhD, with Geraldine Richelson. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1980. 214 pages, $9.95.

EFFECTS OF HORMONES, DRUGS AND CHEMICALS ON TESTICULAR FUNCTION—Volume 1—A. G. Davies, Department of Physiology, The University of Birmingham, The Medical School, Birmingham, England. Eden Medical Research Inc., P.O. Box 51, St. Albans, VT (05478), 1980, 276 pages.

NATIONAL
KIDNEY FOUNDATION
OF SOUTHERN CALIFORNIA

Presents

The 21st Annual Scientific Symposium on

KIDNEY DISEASE

FEBRUARY 28, 1981

Ambassador Hotel
Los Angeles, California

Topics include:

Advances in Renal Hormone-Receptor Interactions

The Use of Hormone Assays in the Diagnosis and Treatment of Clinical Disorders of Renal Function

Therapeutic Aspects of Altered Hormone Function in Renal Failure

Guest Speakers include:

Claude Arnaud, MD, San Francisco; Thomas Berl, MD, Denver; and Mordechai Popovtzer, MD, Jerusalem, Israel

This Symposium has been approved by CMA for 6 Category 1 continuing education credits

For information and advance registration contact:

NATIONAL KIDNEY FOUNDATION OF SOUTHERN CALIFORNIA
6820 La Tijera Blvd., Suite 111
Los Angeles, CA 90045
Phone (213) 641-8152

COCCIDIOIDOMYCOSIS: A Text—Edited by David A. Stevens, MD, Chief, Division of Infectious Diseases, Santa Clara Valley Medical Center, San Jose, California, and Associate Professor of Medicine, Stanford University School of Medicine, and Principal Investigator, Infectious Disease Research Laboratory, Institute for Medical Research of Santa Clara County—In the series: CURRENT TOPICS IN INFECTIOUS DISEASE—Series Editors: William B. Greenough III and Thomas C. Merigan. Plenum Medical Book Company, 227 W. 17th St., New York City (10011), 1980. 278 pages, $28.50.

CONSUMER'S GUIDE TO COSMETICS—Tom Conry under the auspices of the Science Action coalition. Doubleday & Company, Inc., 245 Park Ave., New York City (10017), 1980. 376 pages, $3.95 (paperback).

DIET IN PREGNANCY: A RANDOMIZED CONTROLLED TRIAL OF NUTRITIONAL SUPPLEMENTS—March of Dimes Birth Foundation: Original Articles Series, Volume XVI, Number 3—David Rush, MD, Columbia University; Zena Stein, MB, BCh, New York Psychiatric Institute and Columbia University; and Mervyn Susser, MB, BCh, DPH, FRCP(E), Columbia University. Alan R. Liss, Inc., 150 Fifth Ave., New York City (10011), 1980, 200 pages.

THE DOCTORS' CASE AGAINST THE PILL—Barbara Seaman; with a Foreword by the Boston Women's Health Book Collective. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1980. 239 pages, $6.50 (paperback).

ETHICAL OPTIONS IN MEDICINE—Gregory E. Pence, PhD, Coordinator, Human Values in Medicine, School of Medicine, and Department of Philosophy, University of Alabama. Medical Economics Co., Oradell, NJ (07649), 1980. 221 pages, $17.50.

EVERYWOMAN'S HEALTH: The Complete Guide to Body and Mind—by 17 Women Doctors: Consulting Editor: Douglass S. Thompson, MD, Clinical Professor of Obstetrics and Gynecology and Clinical Associate Professor of Community Medicine, University of Pittsburgh School of Medicine; Clinical Professor, Department of Health Services Administration, University of Pittsburgh Graduate School of Public Health; Medical Director, Ob-Gyn Medical Care Center, Magee-Womens Hospital, Pittsburgh. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1980. 774 pages, $19.95.

THE EXPANDING ROLE OF THE NURSE IN NEONATAL INTENSIVE CARE—Edited by Roger E. Sheldon, MD, Associate Professor of Pediatrics, Chief, Neonatal Section, Department of Pediatrics, University of Oklahoma Health Sciences Center; and Pati Sellers Dominiak, RN, MS, Practitioner-Teacher, Special Care Nursery, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Assistant Professor, Rush University College of Nursing Parent-Child Health Graduate Program—in MONOGRAPHS IN NEONATOLOGY—Thomas K. Oliver, Jr., MD, Series Editor. Grune & Stratton, Inc., 111 Fifth Avenue, New York City (10003), 1980. 320 pages, $17.50.

HANDBOOK OF FIRST AID AND EMERGENCY CARE—Developed by the American Medical Association—Medical Advisors: Gail V. Anderson, MD; Christine E. Haycock, MD, and Stanley M. Zydlo, Jr., MD. Random House, Inc., Dept. FT, 4-6, 201 East 50th Street, New York City (10022), 1980. 234 pages, $5.95 (paperback).

NUTRIENTS TO AGE WITHOUT SENILITY—Abram Hoffer, MD, PhD, and Morton Walker, DPM. Keats Publishing, Inc., P.O. Box 876, New Canaan, CT (06840), 1980. 230 pages, $10.95 (hardcover), $2.95 (paperback).

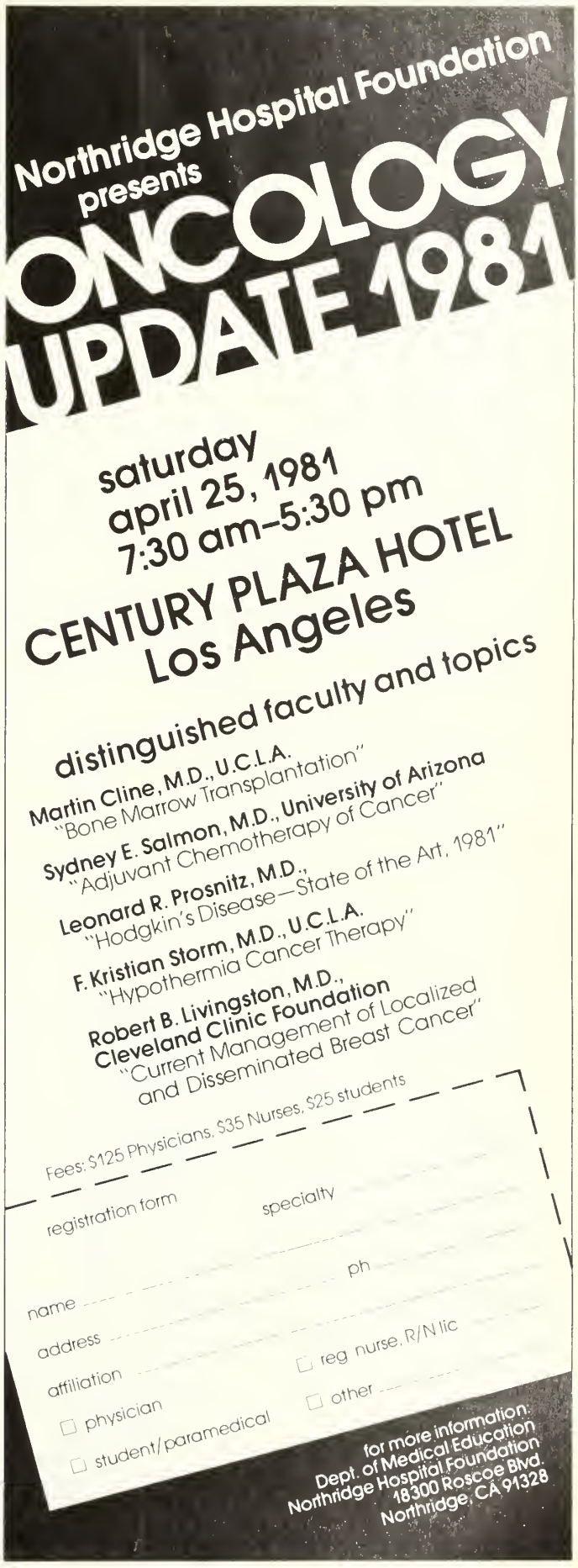
THE PHARMACOLOGICAL BASIS OF THERAPEUTICS—Sixth Edition—Editors: Alfred Goodman Gilman, MD, PhD, Professor of Pharmacology, University of Virginia School of Medicine; Louis S. Goodman, MA, MD, DSc(Hon), Distinguished Professor of Pharmacology, University of Utah College of Medicine, Salt Lake City; and Alfred Gilman, PhD, DSc(Hon), Lecturer in Pharmacology, Yale University School of Medicine, New Haven, Connecticut, Professor Emeritus of Pharmacology, Albert Einstein College of Medicine of Yeshiva University, Bronx, New York; Associate Editors: Steven E. Mayer, MS, PhD, Professor of Medicine, Division of Pharmacology, University of California, San Diego, School of Medicine; and Kennth L. Melmon, MD, Professor of Medicine and Pharmacology, and Chairman, Department of Medicine, Stanford University School of Medicine, Stanford, California. Macmillan Publishing Co., Inc., 866 Third Ave., New York City (10022), 1980. 1,843 pages, $45.00.

PHYSICIAN RECRUITMENT AND THE HOSPITAL—Harry E. Olson, Jr., PhD, Executive Director, Health Planning Continuum, Excelsior, Minnesota. American Hospital Association, P.O. Box 96003, Chicago (60690), 1980. 146 pages, AHA catalog no. 1035, available for $12 to members and $15 to nonmembers (softbound).

PRACTICAL GUIDE TO ANTIMICROBIAL AGENTS—Michael Ginsberg, MD, FRCP (C), Instructor in Medicine, Brown University, Clinical Instructor in Medicine, Harvard Medical School, Consultant in Infectious Disease, Roger Williams General Hospital, Womens and Infants Hospital, and Veterans Administration Medical Center, Providence, Rhode Island; and Ira Tager, MD, MPH, Assistant Professor of Medicine, Harvard Medical School and Peter Bent Brigham Hospital, Boston. The Williams & Wilkins Company, 428 E. Preston St., Baltimore (21202), 1980. 196 pages, $17.95.

PRISONERS OF PAIN—Unlocking the Power of the Mind to End Suffering—Arthur Janov. Doubleday & Co., Inc., 245 Park Avenue, New York City (10017), 1980. 276 pages, $11.95.

SEX BY PRESCRIPTION—Thomas Szasz, MD, psychiatrist in private practice and Professor of Psychiatry, State University of New York at Syracuse. Doubleday & Company, Inc., 245 Park Ave., New York City (10017), 1980. 198 pages, $10.95.



Classified Advertisements

The rate for each insertion is **4.00 per line** (average six words per line) **with five line minimum.**

Box number charge: $2.00 each month.

Classified display rates $40.00 per inch.

Copy for classified advertisements should be received not later than **the fifth of the month preceding issue. All copy must be typed or printed.** • Classified advertisers using Box Numbers forbid the disclosure of their identity. Your inquiries in writing will be forwarded to Box Number advertisers. The right is reserved to reject or modify all classified advertising copy in conformity with the rules of the Advertising Committee.

Please Type or Print Advertising Copy

CLASSIFIED ADVERTISEMENTS ARE PAYABLE IN ADVANCE

PHYSICIANS WANTED

ORTHOPEDIC SURGEON—Board Certified, Orthopedic Surgeon needed at VA Medical Center, Livermore, CA. Ideal living, good climate and clean air. Malpractice insurance not needed. Position available at present. Salary dependent upon experience and qualifications. Contact: John F. Kane, MD, Chief of Staff, VA Medical Center, Livermore, CA 94550. Tel: (415) 447-2560, ext. 204.

WANTED: Univ. trained general surgeon needed to join two other general surgeons in 13 man clinic. Excellent qualifications required. Location: southern Idaho, near excellent outdoor recreation. Write Box 1233, Twin Falls, ID 83301

PHYSICIANS WANTED

GENERAL PRACTITIONERS SPECIALISTS—Are you considering a practice change, please call us, let's talk. We have many opportunities in various West Coast locations. If you would like to join a group, associate or own your own practice we can help. Call us collect at (714) 997-0853, or send CV to Physicians Search Associates, 1201 W. La Veta, Suite No. 209, Orange, CA 92668.

CALIFORNIA, San Jose: Primary Care Physician with experience in Peds. and minor trauma wanted to staff ambulatory care clinic at large teaching hospital in San Francisco Bay Area. Flexible hours, independent contractor status with hourly compensation. For further details, please call or write: Eve Campbell, 1550 The Alameda, No. 314, San Jose, CA 95126. Tele: (408) 293-8881.

GP OR FP for new clinic in the beautiful Black Hills. Ideal setting for many outdoor activities and a place to raise healthy children. Hospital with 49 beds, close association with large medical center. Primary care oriented group practice with starting salary $40,000 plus health, life and malpractice insurance. Contact: Chris Lucas, MD, 209 N. 16th St., Hot Springs, SD 57747. (605) 745-3159.

GENERAL SURGEON NEEDED: Prefer young Bd. elg/cert. surg. Quincy, California. Plumas Co. seat, 85 mi. W of Reno, 87 mi. NW Lake Tahoe. Modern well-equipped 34-bed hosp. 3 family physicians and 2 internists busy now. Cert. surg. help near for time off. Friendly pleasant living with 4 mild and beautiful seasons. Hunting, fishing, skiing, golf. No smog. Magnif. mtn. valley at 3,400 ft. Jr. College. Good shopping. More than 6,000 in town, 18,000 in Co. Call/write Dr. Mark Whitney (916) 283-1710, or Dr. Larry Price (916) 283-0650, Quincy, CA 95971.

(Continued on Page 40)

DEVELOPMENTAL DISABILITIES PROGRAMS

Opportunities are available for internists, family practitioners and psychiatrists to work with developmentally disabled people in State residential communities. Locations from Los Angeles to northern California. Challenging and varied cases, congenial professional environment, excellent civil service benefits.

Hospital Recruitment Program
Dept. of Developmental Services
714 P Street
Sacramento, CA 95814
(916) 322-1221 collect

UCLA FACULTY DEVELOPMENT FELLOWSHIP

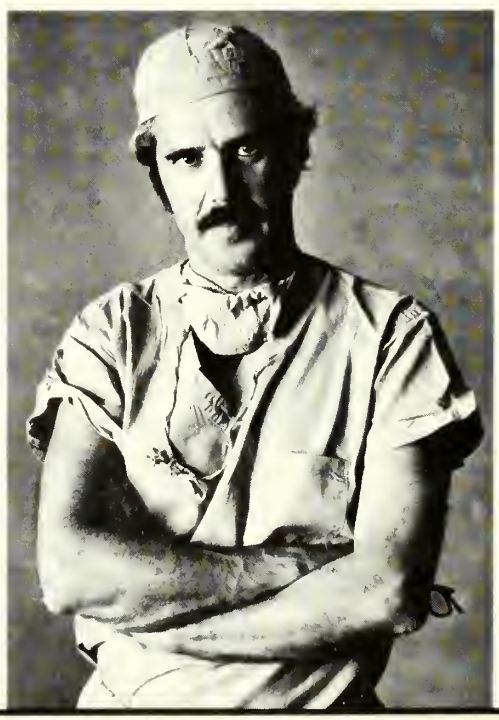
Do you still maintain an intellectual interest in the practice of Medicine? Did your training stop short of your ideal? Are you entertaining an interest in teaching? Would you be willing and able to deliver patient care in the area served by Family Practice at UCLA; i.e. Pediatrics, Nursery, Obstetrics, Medicine, and ICU? If willing to spend twelve months seeking answers to these questions, please write: Wm. MacMillan Rodney, MD, UCLA Family Practice, BH-134 CHS, Los Angeles, CA 90024. UCLA is an equal opportunity affirmative action employer.

We've taken the pain out of establishing your practice.

As a physician you're familiar with ways to alleviate pain. But chances are, your extensive educational process has not prepared you to handle the problems of selecting a location and establishing a successful private practice. National Medical Enterprises' Professional Relations Department has a staff of highly trained people who can help take the anguish out of making this important decision.

If you are familiar with NME you know us as one of America's largest and fastest growing health care companies that owns, operates, and manages acute care facilities that meet or exceed JCAH standards.

NME can provide Board Eligible/Board Certified physicians with private practice opportunities from Seattle, Washington to St. Petersburg, Florida - opportunities that enable you to concentrate on medicine while we assist you through the start-up phase of your new practice.



NME can offer you some of the best equipped health care facilities in the nation along with modern offices, a diverse choice of climates and a community ideally suited to your lifestyle.

Let us take the pain out of establishing a practice for you. Write and send us your curriculum vitae. Let us know your interests and where you want to live and practice. For additional information, contact:

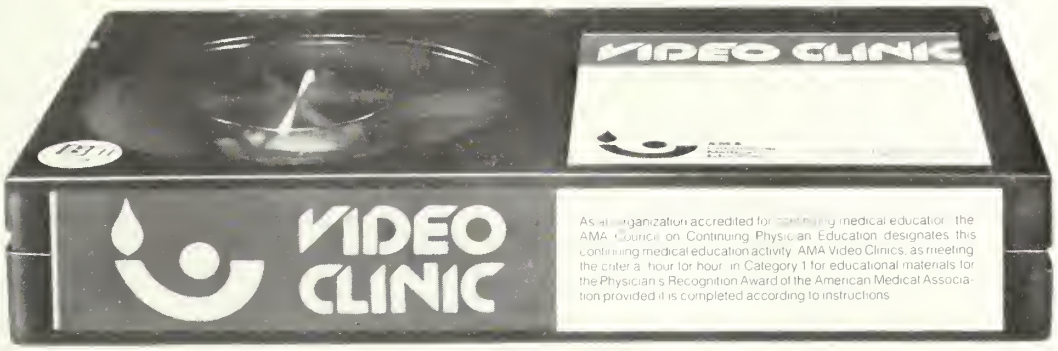
Raymond C. Pruitt
Director, Physician Relations
National Medical Enterprises
11620 Wilshire Blvd.
Los Angeles, California 90025
(213) 479-5526
1-800-421-7470

NME NATIONAL MEDICAL ENTERPRISES, INC.

"The total health care company."

Announcing... FIVE NEW CME VIDEO CLINICS from the AMA

Now . . . choose from 15 top quality programs! The AMA has added five outstanding new programs to its Video Clinic Library: *Acute Gastrointestinal Bleeding, Antibiotic Therapy in Office Practice, The Depressed Patient, Bronchial Asthma, and Alcoholism: Early Diagnosis & Management.* With the addition of these five new Video Clinics to the 10 already available, you have a wide selection from which to choose. To rent or purchase your Video Clinics, use the convenient order form below.



VIDEO CLINIC ORDER FORM

Send order to:
Department of Marketing Communications
American Medical Association
535 North Dearborn Street
Chicago, Illinois 60610
(312) 751-5951

I wish to ☐ buy ☐ rent the following Video Clinics that I have circled below. I understand I will be billed later. I am ☐ am not ☐ an AMA member.

		AMA Member		Nonmember	
		Rental	Purchase	Rental	Purchase
1.	Backache—4 hrs.	$55	$500	$75	$600
2.	Vulvovaginal Problems—5 hrs.	$65	$625	$90	$750
3.	Practical Rheumatology—5 hrs.	$65	$625	$90	$750
4.	The Comatose Patient—3 hrs.	$45	$375	$60	$450
5.	The Multiply Traumatized Patient—3 hrs.	$45	$375	$60	$450
6.	Neurological Examination—6 hrs.	$75	$750	$105	$900
7.	Dizziness—3 hrs.	$45	$375	$60	$450
8.	Headache—2 hrs.	$35	$250	$45	$300
9.	Neck Pain—3 hrs.	$45	$375	$60	$450
10.	Hypertension—3 hrs.	$45	$375	$60	$450
	NEW!				
11.	**Acute Gastrointestinal Bleeding—2 hrs.**	$35	$250	$45	$300
12.	**Antibiotic Therapy in Office Practice—3 hrs.**	$45	$375	$60	$450
13.	**The Depressed Patient—2 hrs.**	$35	$250	$45	$300
14.	**Bronchial Asthma—3 hrs.**	$45	$375	$60	$450
15.	**Alcoholism: Early Diagnosis & Management—3 hrs.**	$45	$375	$60	$450

Terms: Rented Video Clinic tapes must be returned within 15 days from receipt. Net cash 30 days. WJ1/81

Please Print

Name _____

Address _____

City/State/Zip _____

Telephone _____

Please be sure to indicate video cassette format:
☐ U/MATIC PLAYBACK ☐ BETAMAX PLAYBACK I
☐ BETAMAX PLAYBACK II ☐ VHS PLAYBACK

If you do not know the type of playback equipment, please state name of manufacturer and model number:

_____

For group rentals, each participant will be billed at the rate per credit hour of $10 for AMA members or $15 for nonmembers. There is a $15 handling fee for each program ordered. Names, addresses and AMA membership status of each registrant must be included with the order.

Prices subject to change.

(Continued from Page 38)

PHYSICIANS WANTED

OBSTETRICIAN/GYNECOLOGIST WANTED to join the OB/GYN Department of Magan Medical Clinic, Inc., a 31 physician multispecialty group practice located in Southern California near Los Angeles. Call or send CV to Dale H. Weifenbach, MD, Magan Medical Clinic, Inc., 420 W. Rowland St., Covina, CA 91723. (213) 331-6411.

NEW MEXICO: Northwestern. Opportunity available for a physician interested in providing primary care in this modern clinic open 8 a.m.-5 p.m. Monday through Friday. Guaranteed income, liability insurance provided. For details, send credentials to Bill Salmo, Chase Stone Center, Holly Sugar Building, Suite 440, Colorado Springs, CO 80903 or call collect (303) 471-4981.

BEHAVIORAL NEUROLOGY FELLOWSHIPS: Recent graduates of psychiatry and neurology residencies are encouraged to apply for two behavioral neurology fellowships, one designated for a psychiatrist and one for a neurologist, available July 1981 and sponsored by the Department of Neurology, Stanford University School of Medicine, and the Department of Psychiatry (Inpatient Service), Santa Clara Valley Medical Center—a Stanford University Medical School Affiliate. Exciting interdisciplinary approach on Neurobehavioral Unit with emphasis on evaluation and understanding of patients with behavioral problems related to suspected or known neurologic disease. Broad research opportunities. Excellent teaching and supervision with varied patient population. PGY 5—$22,700. An affirmative action/equal opportunity employer. Write: J. William Langston, MD, Santa Clara Valley Medical Center, 751 So. Bascom Ave., San Jose, CA 95128. Telephone (408) 279-5246.

THE SECTION OF EMERGENCY MEDICINE OF THE UNIVERSITY OF ARIZONA HEALTH CENTER is seeking academically oriented emergency physicians for faculty positions in the Section of Emergency Medicine. Applicants are preferred who are trained in emergency medicine, internal medicine, or surgery. Responsibilities include academic, clinical and research endeavors in a growing emergency medicine section. An emergency medicine residency is being planned in the future. If interested, please contact Harvey W. Meislin, MD, Chief, Section of Emergency Medicine, Arizona Health Sciences Center, 1501 N. Campbell Ave., Tucson, AZ 85724. (602) 636-6312. The University of Arizona is an Equal Opportunity Affirmative Action Employer.

Excellent opportunities exist in prime geographical locations throughout the Western, Midwestern and Rocky Mountain states for General and Family Practice Physicians. Access to hunting, fishing, skiing, boating and other excellent recreational activities. Top school systems and warm community atmosphere. Unlimited opportunity to make an impact. Compensation package includes base guarantee, incentives and fringe benefits. Complete medical practice support. The future holds unlimited growth potential. For information contact:

AHS
Advanced Health Systems, Inc.
Professional Placement
17861 Cartwright Road
Irvine, CA 92714
or call toll-free (800) 854-3020
EOE M/F

PHYSICIANS WANTED

OTOLARYNGOLOIST—Solo practice in beautiful Pacific Northwest coastal city. Excellent school system, University in city, abundant recreational opportunities. Must be board certified or eligible, aggressive and hard working. Reply Box 6156, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

GP—I need someone to share my busy practice in primary care adult medicine. Minimal night call. Preventative care stressed. Beautiful northern Idaho location. Call or write Christina Bjornstad, MD, 625 6th Ave., Lewiston, ID 83501. 1 (208) 746-0861.

COALINGA, CALIFORNIA: Rare opportunity in town of 10,000 for solo GP/FP. No night or weekend call. Guarantee, paid malpractice, profit sharing, 90 percent private patients. Contact: Carol Sweig, Western Physicians, 1124 Ballena Bl., Alameda, CA 94501. (415) 521-4110.

CARDIOLOGIST, Board certified or eligible trained in heart catheterization for four man cardiology group, affiliated with large Cardiovascular Center. Referral practice located near Los Angeles. University affiliation available. Immediate partnership, nothing to buy. Equal work, pay and time off. Call (213) 866-3716.

PHYSICIAN—Board certified/eligible Emergency Medicine, Surgery, Pediatrics, Internal Medicine for Emergency service located in sunny Southern California. Full time position with competitive salary, liberal fringe benefits including malpractice insurance and teaching responsibilities. Send CV to Box 6162, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

ANESTHESIOLOGY: Scheduling change necessitates immediate opening for full-time Board Certified anesthesiologist in rural area of Northern California. Modern, well-equipped hospital; excellent opportunity to join growing partnership. Contact Judy Neal (415) 832-6400.

FINANCIAL REWARDS
and
PROFESSIONAL SATISFACTION . . .
. . . plus a whole lot more, Doctor!

We offer physician salaries in all specialties including General Practitioner and Family Practitioner that are among the highest paid in the nation and our benefit package (including malpractice insurance) is unexcelled.

Our quality of care is excellent; our medical facilities are attractive and efficient; and our climate for both living and working is outstanding.

We are one of the largest Federally-approved HMO's in the U.S., and we currently have a few very desirable positions available in the Los Angeles area. If you are interested, please call or write:

INA HEALTH PLAN OF CALIFORNIA
1860 Century Park East
Los Angeles, CA 90067
Phone (213) 553-6677, Extension 364
Attn.: Mr. Yoakam
Director of Physician Services

PHYSICIANS WANTED

VIRGINIA: Primary care physician needed join staff at growing practice in scenic centr Virginia. Enjoy well equipped facility, excelle staff, strong community support, guaranteed l come, excellent linkages with hospitals a other providers in area with growing econom beautiful mountains, large lakes, year rou mild weather, available land and substantial lower cost of living. Locum tenens considere Contact: John Troldl, Administrator, Evingt Medical Center, "P" Drawer 81, Evington, Vi ginia 24550.

(Continued on Page 42)

THE WESTERN Journal of Medicine

Formerly California Medicine

CLASSIFIED RATES

$4.00 PER LINE

(Average six words per line)

FIVE LINE MINIMUM
BOX NUMBERS $2.00 EXTRA

• • •

DISPLAY CLASSIFIED

$40 PER COLUMN INCH

Three column page rate available on request

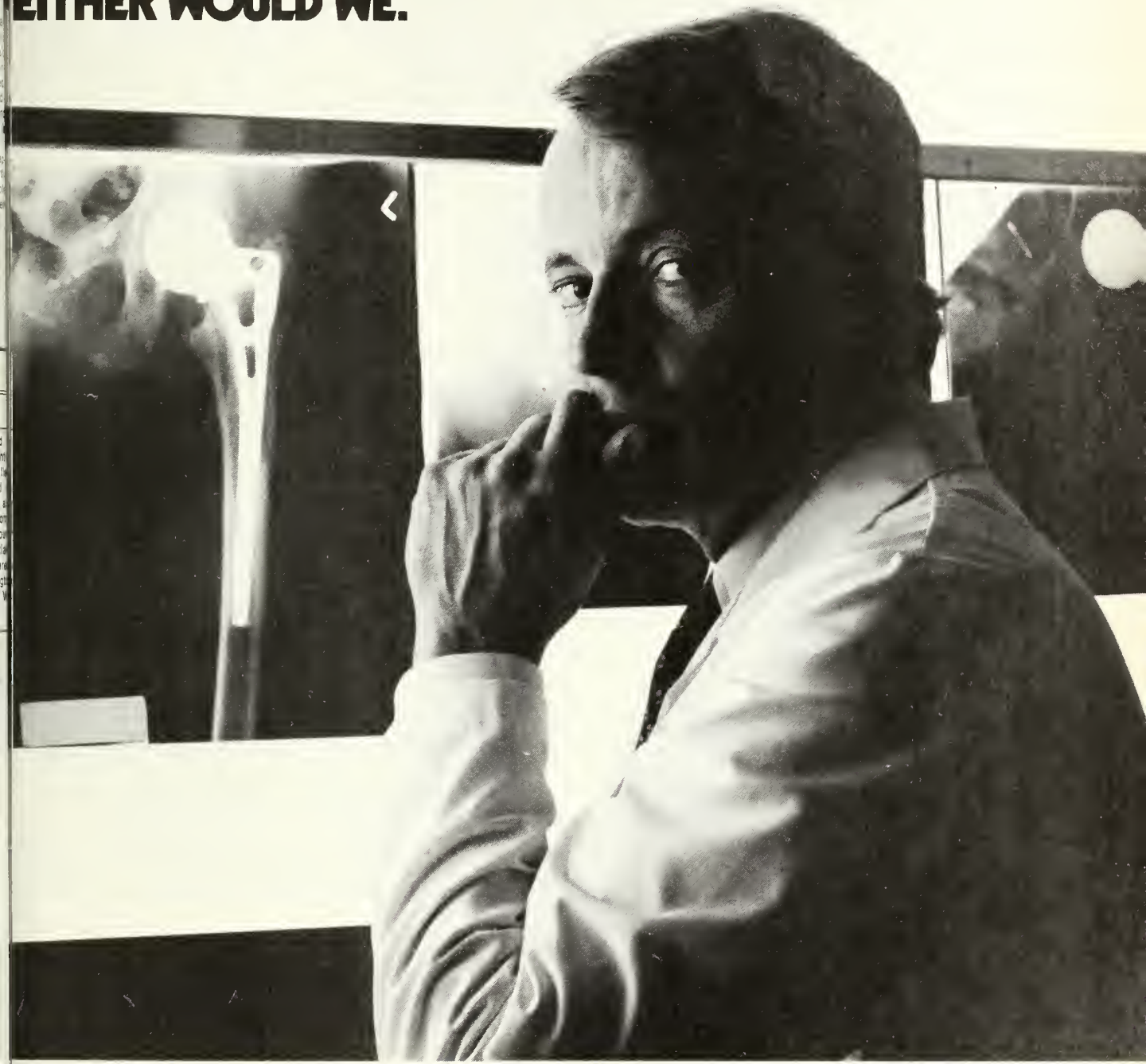
COLUMN WIDTH
1 column 2⅛" • 2 columns 4½" • 3 columns 7"
(Classified Advertising is payable in advance)
Please type or print advertising copy

DEADLINE
1st of Month before publication date

731 MARKET STREET
SAN FRANCISCO, CA 94103 • (415) 777-2000

OULD YOU GUARANTEE THERE WON'T BE PROBLEMS VER THE NEXT 5 YEARS?

EITHER WOULD WE.



Responsible physicians know that despite sound medical judgment and specialized skills, their prognoses are often subject to uncertainty.

You must make allowances for potential adversity and you should expect your professional liability insurance company to do the same.

Responsible medical malpractice insurers, like The Doctors' Company, know that their policyholders' long-range interests are best protected by financial strength and solvency.

That's why we maintain the largest surplus of all the doctor-owned malpractice insurers in the western United States. That's why our earned premium to surplus ratio is the most favorable of all these companies. And that's why we continue to collect surplus contributions from new members.

Future results can't be guaranteed, in the fragile art of medicine or in the volatile business of malpractice insurance. Our allowance for adversity is surplus.

For details about our program, call or write: The Doctors' Company, 233 Wilshire Blvd., Santa Monica, CA 90401. (213) 451-9936. Toll free, (800) 352-7271. Outside California, (800) 421-2368.

THE DOCTORS' COMPANY

AN INTERINSURANCE EXCHANGE
OFFERING MEDICAL MALPRACTICE INSURANCE
TO DOCTORS IN
CALIFORNIA, NEVADA, WYOMING AND MONTANA

(Continued from Page 40)

PHYSICIANS WANTED

EMERGENCY MEDICINE OPPORTUNITIES, full and part-time, in the Rocky Mountain states for career oriented emergency physicians. Excellent compensation and paid professional liability insurance. Send credentials to Mr. William Salmo, Chase Stone Center, Holly Sugar Building, Suite 440, Colorado Springs, CO 80903. Or call toll-free 1 (800) 525-3681 (in Colorado call collect (303) 471-4981).

PHYSICIAN LIBERATION! COMPHEALTH, AMERICA'S OLDEST AND LARGEST LOCUM TENENS COMPANY, can cover your practice while you are away. For more information please write or call us at: Comprehensive Health Systems, 2400 West 7800 South, Suite 202, West Jordan, UT 84084. (801) 566-1666.

DIRECTOR, UNIVERSITY OF UTAH RESIDENCY PROGRAM. Full-time faculty positions, physicians with knowledge and experience in Family Practice. Responsible for intergration and expansion of an established residency program at the University of Utah, EOE. Medical Center, Salt Lake City, UT 84132. C. Hilmon Castle, MD, 50 North Medical Drive, Salt Lake City, UT 84132.

ADMINISTRATIVE DIRECTOR OF RADIOLOGY—Excellent opportunity to join the management staff of a 350 bed hospital located in two separate facilities. Live in Idaho, a beautiful four-season recreation area. Incumbent will work closely with Radiologists and Administration. Will be responsible for all functions including: nuclear medicine, CT, ultrasound, quality control and complete radiological services. Must be ARRT Registered, have a BS degree, and 3-5 years progressive managerial experience, including background in equipment selection and operation. Excellent salary and benefits package. Send résumé to Sharon Gardner, Personnel Manager, Idaho Falls Consolidated Hospitals, 2525 So. Blvd., Idaho Falls, ID 83401. Equal Opportunity Employer M/F/H.

OPHTHALMOLOGY—Southern California buy-in busy, attractive solo practice. Finest phoeco-emulsification and other surgical facilities. Well established in small, warm community. Large enough for two full time doctors. Easy terms. Send cv to Bern, Box 2449, Rancho Santa Fe, CA 92067.

OPHTHALMOLOGIST wanted to take over optometric practice in Laguna Hills, California. Excellent location, next to Leisure World retirement Community. 1,000 sq. ft. suite in 3 bldg. medical complex. A prime opportunity to establish in the fastest growing area in Calif. Call (714) 837-2200 or write P.O. Box 2401, Laguna Hills, CA 92653.

INFECTIOUS DISEASE Specialist wanted to join another busy ID Specialist in private practice in growing city in Northwest. Please send CV to Box 6163, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

GENERAL SURGEON—needed in established multispecialty clinic in beautiful university town. First year guaranteed with full fringe benefits and incentive, new hospital, four season recreation, and ideal family environment. Contact The Budge Clinic, 225 E. 4th North, Logan, UT 84321.

YUBA CITY-MARYSVILLE—Outstanding opportunity for medical practice. Office in established professional building for lease. Growing area. Reasonable terms. Call collect Gayla Stallins (916) 674-1330.

FRESNO-BAKERSFIELD-OXNARD. Family Medical Center, a primary care group practice, has positions available for Bd. Cert./Elig. Gen. Pract. or Internist. Minimum guarantee, partnerships available. New facilities, all administrative services provided. Contact: S. Lee, P.O. Box 8013, Fresno, CA 93747. (209) 252-1618.

GROW WITH US IN SUNNY ARIZONA

The INA Healthplan needs physicians in family practice and most specialties in Tucson and Phoenix. Competitive salaries and comprehensive benefits including a professional development program, retirement plan, and group incentive bonus are provided. If team interaction and casual living interest you, send your CV to:

Professional Relations
INA Healthplan, Inc.
6115 North 7th Street
Phoenix AZ 85014

PHYSICIANS WANTED

SAN FRANCISCO BAY AREA—45-MD multispecialty private group practice established 25 years ago, seeking an orthopedic surgeon for medical/industrial office work to assist our busy 2 physician department in their general orthopedic work. Excellent location in the Santa Clara Valley, 45 minutes from San Francisco, 10 minutes from Stanford University. Send CV to: Walter Saphir, MD, Sunnyvale Medical Clinic, 596 Carroll St., Sunnyvale, CA 94086.

GENERAL INTERNIST. Excellent opportunity with well established 2-man private practice association in sophisticated medical community. Contact David L. Davis, MD, 1400 Florida Ave., Modesto, CA 95350. (209) 527-5063.

THINKING OF RETIRING? MEDICAL DIRECTORSHIPS available, across the USA, any age physician, no fee, malpractice insurance paid, 35 hr/wk, $35 to $40,000/yr., depending on location. List valid licenses, when able to relocate? Where? Please send résumé, including telephone number. To: Fred V. Hrachovina, DO, 1000 Second Ave. South, Minneapolis, MN 55403.

SITUATIONS WANTED

HEMATOLOGIST-ONCOLOGIST needed for busy, aggressive practice of same in Northern California community, one and a half hours from San Francisco. Teaching available. Send CV to Box 6153, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

RADIOLOGIST, 50, CERTIFIED. Previous fellowships in cardiovascular and neuroradiology. Expertise various forms special procedures. 5 years experience neuro CT. Presently director of neuroradiology and special procedure section of large busy university affiliated hospital with faculty appointment. No preference as to location. Write Box 6157, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PULMONARY INTERNIST, University trained, ABIM, trained all phases of pulmonary medicine; seeks practice opportunity; available July 1981. Box 6141, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

RADIOTHERAPIST—Boards, long experience private hospital. Prefer half-time. Northern California. Will consider any California location. Reply Box 6169, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

SITUATIONS WANTED

PHYSICIAN with 10 years experience in preventive and occupational medicine and postgraduate training for 4 years, seeks position in San Francisco/Bay Area in medical outpatient clinic. Write Box 6020, The Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

I AM AN INTERNIST planning to start a practice in a growing area 2½ hrs. from San Francisco and 1 hr. from skiing. Would like to find internist with similar goals of generous time off, to share initial investment for furnishings etc. and to share subsequent overhead and call. Reply Box 6160, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PATHOLOGIST, 45, certified AP-CP, excellent references, seeks relocation to San Francisco-San Jose area for permanent full-time or part-time practice. Box 6110, The Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

CARDIAC REHABILITATION: Internist with ACSM Program Director Certification and 2 year University Fellowship in Clinical Exercise Physiology and Cardiac Rehabilitation, and 1 year experience in designing and working as Medical Director of a private Cardiac Rehabilitation Clinic seeks a position as Medical Director of Exercise Physiology and Cardiac Rehabilitation Facility, preferably with university affiliation. Box 6164, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

WOMAN PHYSICIAN in early sixties, in good health, seeks part-time position, 1-2 days/week, in psychiatry and/or general medicine in Catholic hospital, institution or office within 50 mi. radius of San Francisco or Truckee in California. Practice must be under physician willing to supervise, as probationary requirement of BMQA. Write to: Physician, Box 6165, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

GASTROENTEROLOGIST, 37, ABIM, American Grad. trained in all phases of endoscopy, additionally in laparoscopy, PTC, ERCP and esophageal motility. Prefer California and Southwestern U.S. Presently on faculty, available immediately. Box 6166, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

INTERNIST—30, ABIM certified, moving to San Diego July 1981. Seeks position in Internal Medicine. Reply Box 6167, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

INFECTIOUS DISEASE-INTERNIST. University trained, 30, ABIM certified. ID Board eligible. Desires opportunity in Infectious Disease/Internal Medicine in or near San Diego. Available July 1981. N. Kollisch, MD, 33 Pond Ave., Brookline, MS 02146. Tel (617) 566-0875.

GASTROENTEROLOGIST, 35, broad experience in clinical gastroenterology and all major procedures. Desire Southern California area, available July 1981. Jack D. Goldin, MD, 1274 Ocean Parkway, Brooklyn, NY 11230.

RADIOLOGISTS: Plan your 1981 vacation early. Board Certified coverage for your practice. Licensed all western states. Reserve early for best selection of dates. For further information reply c/o Box 6159, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

ADMIN. ASST./EXECUTIVE SECRETARY seeks exciting opportunity in medical or academic setting. Twenty years experience includes 4 years foreign employment and travel. Excellent organization, communication, interpersonal and secretarial skills. Reply Box 6168, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

LOCUM TENENS SERVICE

WESTERN PHYSICIANS REGISTRY offers coverage for vacation or continuing education. To participate as temporary physician or to arrange coverage for your practice, contact: Carol Sweig, Director, 1124 Ballena Bl., Alameda, CA 94501. (415) 521-4110.

MEDICAL PRACTICES AVAILABLE

BUYING or SELLING any type Medical Practice contact California Professional Practices, 2555 Huntington Dr., Suite D, San Marino, CA 91008. (213) 796-9262 or Agent Mr. Reilly (805) 543-4782 or Cliff Rauch (714) 997-0853.

PROFESSIONAL PRACTICE OPPORTUNITIES—Dermatology, Internal, Ophth, EENT, ENT, Otolaryngology, Family, Pediatrics, others available. To buy or sell any type practice, partnership, or for placement contact Mary Bradshaw, 21 Altamount, Orinda, CA 94563. (415) 376-0762.

MEDICAL / LABORATORY / PHARMACY SPACE AVAIL. in Lincoln, California, near Sacramento. Developer is seeking Multi-discipline Medical Practitioners to locate within new 21,000 sq. ft. Medical Ctr. to be completed February 1981. Facilities will include lab, x-ray, and pharmacy. Excellent growth area. Hewlett Packard and Shugart & Assoc. Electronics Companies building in vicinity with 5,000 to 15,000 new employees. Will build to suit. Contact R. S. Management Co., 541 Jefferson Ave., Suite 107, Redwood City, CA 94063. Call (415) 365-6400.

PSL

PRACTICE SALES & LOCATIONS

BUY • SELL • LEASE
EVALUATIONS • FINANCE
17942 Skypark Circle, Ste D, Irvine, CA 92714
(714) 641-9203

General/Family—Internal Medicine

Industrial/Multi-Specialty Clinics and other specialties

LOCATIONS

For Lease—Medical Bldgs—For Sale

APPRAISALS

Comprehensive practice and property appraisals

ASSOCIATESHIPS

Placement services—Partnerships
Financing, Practice/Property Management

PRACTICES FOR SALE

RENO, NEVADA—FAMILY PRACTICE. 2 years old and still growing. Fully equipped leased office in medical complex across from hospital. Asking $40,000. ½ down—I will finance the rest at 10%. Call (702) 322-6947 or (702) 322-3892.

HAWAII: Resort area of Maui, 99 percent collection rate: cash clientel, no hospital work necessary, annual net: $50,000 to $100,000. For information write Darnell Richey, MD, P.O. Box 1476, Kihei, MI 96753 or call (808) 879-7447.

MEDICAL EQUIPMENT FOR SALE

SYSTEC TEMPERATURE MONITOR, $200.00; autogenic myograph (1500), $350.00. Virginia Flanagan, MD, 13320 Riverside Drive, No. 112, Sherman Oaks, CA 91423. Phone: (213) 995-4233.

BIO-DYNAMICS THYROTEK T3-T4, Unimeter 300 Can Do SMA 21, Select-A-Fuge 24, Unibac Enviromental System Chamber Bacterial Developer, Hyperion Diluter Dispenser Model 365A Serial No. 2004, Royco Cell-Crit 920-A Coincidence Corrected, Royco Hemoglobin No. 720A Hemoglobinometer. All in prime condition. Please call Albert Hertz, 247 North Larchmont Blvd., Los Angeles, CA 90004. (213) 461-9373.

WORKING OFFICE SUPPLIES for immediate sale (rapidly growing area). Could start practice immediately on site. Beautiful Puget Sound Area—Seattle Suburb. Close to skiing—Mount Rainier—University of Washington. Owner/practitioner is accepting Administrative position in distant state. Box 6168, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

LEGAL COUNSEL

SAMUEL SPITAL, ESQ.
1200 Third Avenue, Suite 1200
San Diego, CA 92101, (714) 231-4848

Former DEPUTY ATTORNEY GENERAL representing the Board of Medical Quality Assurance and Dept. of Health. Now specializing in B.M.Q.A. and defense malpractice matters throughout California.

Classified Advertisements

USE THIS ORDER BLANK TO ADVERTISE PHYSICIAN OPPORTUNITIES, SITUATIONS WANTED, PRACTICES, OFFICES, MEDICAL EQUIPMENT, ETC.

CLOSING DATE for copy and advance payment: 5th of month PRECEDING date of issue.

The rate for each insertion is **$4.00 per line** (average six words per line) **with five line minimum.**

DISPLAY RATES. $40.00 per inch.

Box number charge: $2.00 each month.

CLASSIFIED ADVERTISEMENTS ARE PAYABLE IN ADVANCE. PLEASE TYPE OR PRINT AD COPY.

THE WESTERN Journal of Medicine

731 MARKET ST. • SAN FRANCISCO, CA 94103 • TEL. (415) 777-2000, EX. 220

_____

_____

_____

_____

_____

Name _____ **Address** _____

Enclosed is $_____ for _____ Insertion(s).
(No. Mos.)

Check one: ☐ Please include my name and address in ad
☐ Please assign a box number ($2.00 additional for each month's insertion)

Read across specialty lines.

Each month the WESTERN JOURNAL provides an excellent, quick way
for busy physicians to keep abreast
of what is happening in other fields of medicine.
It seeks also to offer a balanced fare of scientific and social progress,
with something in every issue for students,
scholars, practitioners, academicians, researchers and Medicine's political leaders.

The WESTERN JOURNAL lets you read across specialty lines.

THE WESTERN
Journal of Medicine

Please mail this coupon with enclosed payment to:
THE WESTERN JOURNAL OF MEDICINE—Circulation Department
731 Market Street, San Francisco, California 94103

WJ1/81

Subscriptions, U.S. and Canada $10 All other countries $18

Enclosed is $_____ to cover _____ subscriptions. Subscription renewal ☐

Send subscription

TO: _____
Street
City State Zip
Specialty
Gift Card to read "From _____"
Regular subscription ☐ Foreign subscription ☐

TO: _____
Street
City State Zip
Specialty
Gift Card to read "From _____"
Regular subscription ☐ Foreign subscription ☐

(Continued from Page 25)

Fndn., American Heart Assn., American Lung Assn., Nat'l Critical Care Institute of Education, Vascular Disease Fndn. at Mission Bay Hilton, San Diego. Friday-Sunday. $250. Contact: CREF, P.O. Box 33185, San Diego 92103.

February 21—**Workshop in Advanced Electrocardiography.** PMC. Saturday. 7 hrs. $110.

February 21-28—**Metabolism and Endocrinology.** Univ. of Washington School of Medicine at Kona Surf Hotel, Kona, Hawaii. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

February 21-28—**Practical Neurology.** Univ. of Washington School of Medicine at Ilikai Hotel, Honolulu. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

February 23-26—**Advances in Clinical Practice of Hematology/Oncology.** Scripps Clinic and Research Fndn. at Vacation Village, San Diego. Monday-Thursday. 25 hrs. $290. Contact: Nomi Feldman, 2321 Morena Blvd., San Diego 92110. (714) 275-0650.

February 25—**Hospital Acquired Infections.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday. 7½ hrs. Contact: Program Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

February 27-March 1—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Sahara Hotel, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

March 2-4—**Immunology.** STAN. Monday-Wednesday. 13 hrs. $225.

March 2-4—**Dermatologic Problems of Interest to Internists.** STAN at Marriott's Rancho Las Palmas Resort, Rancho Mirage. Monday-Wednesday. 15 hrs. $200.

March 2-4—**Basic Neuroscience and Biobehavioral Science.** See Psychiatry, March 2-4.

March 4-7—**Immunology and Clinical Practice of Allergy—5th Annual Course.** UCSD at Hilton, San Diego. Thursday-Saturday. 20 hrs.

March 7-11—**American Academy of Allergy.** Hilton Hotel, San Francisco. Saturday-Wednesday. 32 hrs. $125, nonmembers. Contact: Donald McNeil, Exec. Dir., AAA, 611 E. Wells St., Milwaukee, WI 53202. (414) 272-6071.

March 8-11—**Consultants' Course in Dermatology.** UCSF at Ahwahnee Hotel, Yosemite. Sunday-Wednesday.

March 11—**Common Fractures and Joint Injuries.** LLU. Wednesday. 4 hrs. $30.

March 13-14—**Cardiac Ischemia and Arrhythmias—Current Concepts for Diagnosis and Treatment.** International Medical Education Corp. at Sheraton Fisherman's Wharf, San Francisco. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

March 13-14—**Diagnosis and Treatment of Venous Thromboembolism.** PMC. Friday-Saturday. 10 hrs. $125.

March 15-18—**Symposium on Gastroenterology.** UCSF at Ahwahnee Hotel, Yosemite. Sunday-Wednesday.

March 15-19—**American College of Cardiology.** San Francisco. Sunday-Thursday. Contact: ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

March 23-April 4—**Intensive Review of Internal Medicine—29th Annual.** USC. Two weeks.

March 27-28—**Gastroenterology for the Practicing Internist.** UCLA at Palm Springs. Friday-Saturday.

March 27-29—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Aladdin Hotel, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

March 29-April 1—**Basic Cardiology for the Practicing Physician.** UCSF at Hyatt, Lake Tahoe. Sunday-Wednesday. 13 hrs. $175.

April 4-5—**Infectious Disease for the Practicing Internist.** UCLA at Palm Springs. Saturday-Sunday.

April 5-8—**Cosmetics for the Clinician: A Symposium for Dermatologists.** UCD at Ahwahnee Hotel, Yosemite. Sunday-Wednesday.

April 6-15—**Cardiology for the Consultant: A Clinician's Retreat.** American College of Cardiology at Rancho Santa Fe. 10 days. Contact: Registration Sec., Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

April 8—**Cardiology Symposium.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6 hrs. $35. Contact: Cont. Med. Ed., N. T. Enloe Memorial Hosp., 5th Ave and The Esplanade, Chico 95926. (800) 822-8102, ext. 7375.

April 8—**Annual Physicians' Cardiovascular Symposium.** American Heart Assn., Central Valley Chapter, at Hilton, Fresno. Wednesday. Contact: Genny Berry, AHA, Central Valley Chap., 3835 N. West Ave., Fresno 93705. (209) 224-8215.

April 8-10—**Update in Pediatric Pulmonary and Intensive Care.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. Contact: Prog. Coordinator, Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

April 8-11—**California Blood Bank System—29th Annual Meeting.** Hyatt Airport Hotel, Los Angeles. Wednesday-Saturday. Contact: Mrs. Beverley Hayhurst, Exec. Sec., CBBS, P.O. Box 5401, San Bernardino 92412. (714) 885-6503.

April 10-12—**Cardiac Ischemia and Arrhythmias—Current Concepts for Diagnosis and Treatment.** International Medical Education Corp at Sheraton, Anaheim. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

May 1-2—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Sheraton Fisherman's Wharf, San Francisco. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

May 2-3—**Practical Dermatology.** UCLA at Santa Barbara. Saturday-Sunday.

May 6—**Respiratory.** St. Francis Medical Center, Lynwood. Wednesday. 6 hrs. Contact: Allan M. Hoffman, EdD, Dir. of Med. Ed., St. Francis Med. Ctr., 3630 Imperial Highway, Lynwood 90262. (213) 603-6174.

May 6—**Thyroid '81.** Hospital of the Good Samaritan at Bonaventure Hotel, Los Angeles. Wednesday. 7 hrs. Contact: Mary Jane Thompson, Hosp. of the Good Samaritan, 616 S. Witmer St., Los Angeles 90017. (213) 488-8908.

May 7-9—**Cardiovascular Emergencies.** American College of Cardiology and PMC at Mark Hopkins Hotel, San Francisco. Thursday-Saturday. 18 hrs. Contact: Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

May 8-10—**Cardiac Ischemia and Arrhythmias—Current Concepts for Diagnosis and Treatment.** International Medical Education Corp. at Sahara Hotel, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

May 18-22—**Advances in Internal Medicine.** UCSF at Hyatt on Union Square, San Francisco. Monday-Friday.

May 23-30—**Allergy and Immunology.** Univ. of Washington School of Medicine at Wailea Beach, Maui, Hawaii. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle 98195.

May 31-June 4—**Internal Medicine for the Generalist—1981.** UCSD at Hilton, San Diego. Sunday-Thursday. 23 hrs.

OBSTETRICS AND GYNECOLOGY

January 25-30—**Obstetrics-Gynecology Update: 1981.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Friday.

January 26-30—**10th Annual Review Course in Obstetrics and Gynecology.** USC at Hilton, Pasadena. Monday-Friday. 36 hrs. $400.

February 7-8—**Obstetrical and Gynecological Forum.** Los Angeles Obstetrieal and Gynecological Society at Beverly Hilton, Beverly Hills. Saturday-Sunday. Contact: Dee Davis, Exec. Sec., LAOGS, 5820 Wilshire Blvd., Los Angeles 90036. (213) 937-5514.

April 4-11—**Current Concepts in Ob/Gyn.** Univ. of Washington School of Medicine at Kona Surf Hotel, Kona, Hawaii. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

April 10-11—**26th Annual T. Hart Baker, MD, Obstetrics and Gynecology Symposium.** Southern Calif. Permanente Medical Group at South Coast Plaza Hotel, Costa Mesa. Friday-Saturday. Contact: Lilia M. Guerrero, SCPMG, Dept. of Ed. and Researeh, 4747 Sunset Blvd., 4th Fl., Los Angeles 90027. (213) 667-4241.

April 25-30—**American College of Obstetricians and Gynecologists.** Convention Center, Las Vegas. Saturday-Thursday. Contact: W. H. McDannel, Convention Mgr., ACOG, 1 E. Wacker Dr., Suite 2700, Chicago 60601. (312) 222-1600.

May 11-13—**Recent Advances in Obstetrics and Gynecology.** UCSD at Vaeation Village, San Diego. Monday-Wednesday. 18 hrs.

PEDIATRICS

January 25-28—**6th Annual Pediatric Winter Ski and Study Symposium.** Ameriean Academy of Pediatrics, Calif. Chap. 2, at Mammoth Mountain. Sunday-Wednesday. $160, members; $185, nonmembers. Contact: Calif. Chap. 2, AAP, P.O. Box 2134, Inglewood 90305. (213) 757-1198.

February 4-6—**Children With Heart Disease.** See Medicine, February 4-6.

February 17-20—**Epilepsy in Childhood and Adolescence—32nd Annual Western Institute on Epilepsy.** See Medieine, February 17-20.

March 5-7—**Advances in Pediatrics.** Children's Hospital Medieal Center of Northern Calif. at Sahara Hotel, South Lake Tahoe. Thursday-Saturday. Contact: Gretchen Hayes, Med. Staff Office, CHMC, 51st and Grove Sts., Oakland 94609. (415) 428-3334.

March 12-15—**Clinical Pediatrics.** American Academy of Pediatrics, Calif. Chap. 2, at Hilton Riviera, Palm Springs. Thursday-Sunday. $160, members; $185, nonmembers. Contact: Calif. Chap. 2, AAP, P.O. Box 2134, Inglewood 90305. (213) 757-1198.

April 3-4—**Pediatric Topics.** UCD at Red Lion Motor Inn, Saeramento. Friday-Saturday.

April 8-10—**Update in Pediatric Pulmonary and Intensive Care.** See Medieine, April 8-10.

May 2-3—**The Physician and the Handicapped Child: New Directions.** American Academy of Pediatrics and State Dept. of Education at Sacramento. Saturday-Sunday. Contact: Peter Miller, MD, Marin Co. Civic Ctr., Rm. 280, Dept. of Health and Human Services, San Rafael 94903. (415) 499-6877.

May 4-8—**11th Annual Review of Pediatrics.** USC. Monday-Friday. $300.

May 6-8—**Care of the Sick Newborn—6th Annual Symposium.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. Contaet: Prog. Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

May 13—**Genetic Counseling.** LLU. Wednesday. 4 hrs. $30.

May 14-16—**Advances in Pediatrics.** UCSF at Mark Hopkins Hotel, San Francisco. Thursday-Saturday.

May 20-25—**Pediatrics for the Primary Care Physician and All That Jazz.** UCD at Sacramento. Wednesday-Monday.

PSYCHIATRY

January 25-31—**7th Annual Midwinter Program in Continuing Education for Psychiatrists.** UCD at Hyatt Lake Tahoe, Incline Village. One week. 26 hrs.

January 30-31—**Heinz von Foerster on Cybernetics, Language, and Understanding.** Mental Research Institute, Palo Alto. Friday-Saturday. 12 hrs. $100. Contaet: MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

March 2-4—**Basic Neuroscience and Biobehavioral Science.** STAN. Monday-Wednesday. 15 hrs. $225.

March 4-8—**7th International Gender Dysphoria Symposium.** Univ. of Nevada School of Medicine and Harry Benjamin International Gender Dysphoria Assn. at Cal-Neva Lodge, Lake Tahoe. Wednesday-Sunday. $150. Contaet: Marjorie Cutler, Cont. Med. Ed., College Inn, Univ. of Nevada, Reno 89557. (702) 784-4046.

April 3-5—**Cults, Religiosity and the Adolescent.** UCSF. Friday-Sunday.

RADIOLOGY AND PATHOLOGY

January 19-23—**Interventional Radiologic Techniques: Computed Tomography and Ultrasonography.** UCSF at Fairmont, San Francisco. Monday-Friday. $350.

January 19-24—**Review Course in Clinical Ob, Gyn, and Histological Pathology.** Memorial Hospital Medical Center-UCI Center for Health Education at Newporter Inn, Newport Beach. Monday-Saturday. 41 hrs. Contact: Program Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

January 21-23—**8th Annual Postgraduate Course in Genitourinary Pathology.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beaeh. Wednesday-Friday. 22½ hrs. Contact: Program Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

January 24-31—**International Diagnostic Radiology Conference.** UCSF at Maui Surf Hotel, Maui, Hawaii. One week.

January 26-30—**Tumorous Conditions of the Bones and Soft Tissues.** American Society of Clinieal Pathologists at San Diego. Monday-Friday. 37½ hrs. $500, ASCP members; $600, nonmembers. Contact: Admin. Asst., Education Ctr., ASCP, 2100 W. Harrison St., Chicago 60643. (312) 738-1336.

January 30-February 1—**33rd Annual Midwinter Radiological Conference.** Los Angeles Radiologieal Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. $150. Contact: John Kassabian, MD, 100 Congress St., Pasadena 91105.

February 4-6—**Recent Progress in Diagnostic Laboratory Immunology.** Seripps Clinie and Research Foundation at Vacation Village, San Diego. Wednesday-Friday. 24 hrs. $250. Contaet: Nomi Feldman, 2321 Morena Blvd., San Diego 92110. (714) 275-0650.

February 9-12—**Molecular Basis of Cell-Cell Interaction.** Scripps Clinic and Research Foundation at Islandia Hyatt, San Diego. Monday-Thursday. 24 hrs. $165. Contact: Nomi Feldman, 2321 Morena Blvd., San Diego 92110. (714) 275-0650.

February 9-13—**New Horizons in Laboratory Medicine.** Univ. of Nevada School of Medicine and American Soc. of Clinical Pathologists at Sahara, Lake Tahoe. Monday-Friday. Contact: Marjorie Cutler, Cont. Med. Ed., College Inn, Univ. of Nevada, Reno 89557. (702) 784-4046.

February 11—**Neuroradiology—Its Use, Indications and Values in Strokes, Tumors and Head Trauma.** LLU. Wednesday. 4 hrs. $30.

February 18-20—**Anaerobic Bacteriology Methods.** Memorial Hospital Medieal Center-UCI Center for Health Edueation, Long Beaeh. Wednesday-Friday. 15 hrs. Contaet: Program Coordinator, Ctr. for Health Ed., 2801 Atlantie Ave., Long Beach 90801. (213) 595-3811.

February 25-27—**Minicomputers, Microcomputers and Big Computers.** American Society of Clinical Pathologists at

Monterey. Wednesday-Friday. 19½ hrs. Contact: Admin. Asst., Education Center, 2100 W. Harrison St., Chicago 60612. (312) 738-1336.

February 27-March 1—**Neuroradiology.** USC. Friday-Sunday. 20 hrs. $200.

February 28—**Cytology Workshop.** UCLA. Saturday.

March 4-7—**Sierra Radiology Conference—2nd Annual.** Sacramento Radiology Research and Education Foundation and Northern Calif. Radiological Society at North Lake Tahoe. Wednesday-Saturday. 18 hrs. $245. Contact: Michael H. Reid, PhD, MD, Sacramento Radiology Research and Education Fndn., P.O. Box 161112, Sacramento 95816.

March 6-8—**Current Approaches to Radiation Oncology, Biology and Physics.** UCSF at Fairmont Hotel, San Francisco. Friday-Sunday.

March 8-13—**19th National Conference on Breast Cancer.** See Cancer, March 8-13.

March 9-13—**Diagnostic Radiology.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday. $350.

March 13-19—**College of American Pathologists/American Society of Clinical Pathologists—Joint Spring Meeting.** Town and Country, San Diego. Friday-Thursday. Contact: Joan Lipe, CAP, 7400 N. Skokie Blvd., Skokie, IL 60077. (312) 677-3500.

March 14-15—**B-Scan Ultrasonography: Update.** UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday.

April 11-18—**Hawaii Imaging Conference.** American College of Medical Imaging at Kauai Surf Hotel, Kauai, Hawaii. One week. 23½ hrs. Contact: ACMI, P.O. Box 27188, Los Angeles 90027. (213) 275-1393.

April 25—**Cytology Workshop.** UCLA. Saturday.

May 2-9—**Pathology.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

May 24-29—**The Pathologist as a Clinical Consultant.** UCD at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

Postgraduate Videotape Programs in Diagnostic Radiology. Developed by Dept. of Radiology, UCSF. 27 programs in all aspects of diagnostic radiology. Outstanding national and international guest lecturers in addition to UC staff present basic approaches to radiographic interpretation and technique as well as new research and clinical advances. Contact: Radiology Postgraduate Ed. Section, UCSF, Dept. of Rad., Rm. M396, San Francisco 94143. (415) 666-5731, between 7:00 a.m. and 4:00 p.m.

SURGERY

January 21-23—**Sierra Traumatological Society—10th Annual Meeting.** Bear Valley. Wednesday-Friday. 6 hrs. Contact: Sierra Traumatological Soc., P.O. Box 230, Stockton 95201. (209) 466-9535.

January 23-24—**Third Annual Postgraduate Course in Surgery.** UCD at Point West Hotel, Sacramento. Friday-Saturday. 14 hrs. $85.

January 23-24—**Vitrectomy Workshop.** Jules Stein Eye Institute, Los Angeles. Friday-Saturday. 16 hrs. $500. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024.

January 25-28—**Society of Thoracic Surgeons—17th Annual Meeting.** Bonaventure Hotel, Los Angeles. Sunday-Wednesday. Contact: W. G. Purcell, Bus. Mgr., STS, 111 E. Wacker Dr., Chicago 60601.

January 25-30—**Assembly in Surgery—4th Annual.** UCSD at Sheraton Harbor Island Hotel, San Diego. Sunday-Friday. 28 hrs.

February 1-7—**Otolaryngology Update.** Sacramento Society of Otolaryngology and Maxillo-Facial Surgery at Hawaii. One week. 26 hrs. $350. Contact: Sacramento Soc. of Otolaryn-

The Answer to Medical Information Management Problems MIMS™

HELIO SYSTEMS

A Division of Spectrum Management, Inc.
2195 Zanker Rd. • San Jose, CA. 95131

QUESTIONING THE NEED FOR A COMPUTER IN YOUR HEALTH CARE GROUP?

WE CAN HELP . . .

Just as a physician would not prescribe a remedy for a patient without an accurate and thorough diagnosis of symptoms, HELIOSYSTEMS does a complete analysis of the physician's information management problems before presenting the solution.

Our analysis may show that you really don't need a computer in your office . . . we'll tell you.

Let us answer some questions for you.

We are HELIOSYSTEMS . . .

GET THE ANSWER . . . CALL US
(408) 946-6450

gology and Maxillo-Facial Surgery, P.O. Box 3213, El Macero 95618.

February 4-6—**Current Thinking in the Management of Ocular and Adnexal Tumors.** UCSF. Wednesday-Friday.

February 5-7—**Aesthetic Rhinoplasty and Nasal Reconstruction.** UCLA. Thursday-Saturday.

February 6-8—**National Symposium on Hair Replacement Surgery.** American Academy of Facial Plastic and Reconstructive Surgery and American Society for Dermatologic Surgery at Ramada Inn, Beverly Hills. Friday-Sunday. Contact: Drs. Richard Fleming, Toby Mayer, Peter Goldman, 9730 Wilshire Blvd., Ste. 216, Beverly Hills 90212.

February 8-10—**The Mandible: Surgical Treatment of Congenital and Acquired Deformities.** UCLA. Sunday-Tuesday.

February 10-13—**American Endocurietherapy Society—3rd Annual Midwinter Meeting.** See Cancer, February 10-13.

February 14-20—**Neurological Surgery of the Ear and Skull Base—3rd International Workshop.** Ear Research Institute at Newporter Inn, Newport Beach. One week. 32 hrs. $500. Contact: Derald E. Brackmann, MD, Neurological Workshop, ERI, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

Februry 20-22—**Pathophysiology and Techniques of Cardiopulmonary Bypass.** See Medicine, February 20-22.

February 23-25—**American Society for Surgery of the Hand—36th Annual Meeting.** Las Vegas. Monday-Wednesday. Contact: ASSH, 2600 S. Parker Rd., Suite 132, Aurora, CO 80014. (303) 755-4588.

February 26-March 3—**American Academy of Orthopaedic Surgeons.** Convention Center, Las Vegas. Thursday-Tuesday. Contact: AAOS, 444 N. Michigan Ave., Chicago 60611.

March 1-6—**Symposium on Facial Surgery.** Sacramento Society of Otolaryngology and Maxillo-Facial Surgery at South Lake Tahoe. Sunday-Friday. 26 hrs. $35. Contact: Sacramento Soc. of Otolaryngology and Maxillo-Facial Surgery, P.O. Box 3213, El Macero 95618.

March 1-13—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. 13 days. Contact: Mrs. Mona Bolton, ERI, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

March 5-7—**Calculi.** American Urological Association at Sheraton Harbor Island Hotel, San Diego. Thursday-Saturday. Contact: AUA, Office of Education, Texas Med. Ctr., 4th Fl-Inst. of Religion Bldg., 1129 Wilkins, Houston, TX 77030.

March 6-7—**Ophthalmology Update.** UCD, PMC, UCSF, STAN at Sheraton Palace, San Francisco. Friday-Saturday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062.

March 11—**Common Fractures and Joint Injuries.** LLU. Wednesday. 4 hrs. $30.

March 21-22—**ECG Course for Oral and Maxillofacial Surgeons.** UCSF. Saturday-Sunday.

March 22-April 3—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. 13 days. Contact: Mrs. Mona Bolton, ERI, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

March 25-28—**4th Annual U.S. IOL Symposium.** American Intra-Ocular Implant Society at Century Plaza Hotel, Los Angeles. Wednesday-Saturday. Contact: Debbi Miller, Dir. of Mtg. Services, Am. Intra-Ocular Implant Soc., P.O. Box 3140, Santa Monica 90403. (213) 829-7317.

March 26-29—**Pediatric Surgery of the Head and Neck: A Frontier Symposium.** The Institute for Medical Education and Research and UCSD at Silverado Country Club and Resort, Napa Valley. Thursday-Sunday. 20 hrs. Contact: The Institute for Medical Education and Research, 135 Dickinson St., San Diego 92103.

March 28-29—**Common Problems in Urologic Medicine: Initial Evaluation and Management.** UCSF. Sunday-Monday.

April 4-8—**Seminar on Controversial Surgery—18th Annual.** UCLA at Hilton Riviera, Palm Springs. Saturday-Wednesday. 18 hrs. $295.

April 5-10—**Management of Maxillofacial Trauma.** Sacramento Society of Otolaryngology and Maxillo-Facial Surgery at South Lake Tahoe. Sunday-Friday. 32 hrs. $400. Contact: Sacramento Soc. of Otolaryngology and Maxillo-Facial Surgery, P.O. Box 3213, El Macero 95618.

April 8—**Urology.** St. Francis Medical Center, Lynwood. Wednesday. 6 hrs. Contact: Allan M. Hoffman, EdD, Dir. of Med. Ed., St. Francis Med. Ctr., 3630 Imperial Highway, Lynwood 90262. (213) 603-6174.

April 8-11—**Facial Plastic Surgery Symposium.** UCSF. Wednesday-Saturday.

April 8-12—**Symposium on Vascular Surgery—9th Annual.** UCLA at Hilton Riviera, Palm Springs. Wednesday-Sunday. 18 hrs. $315.

April 9-10—**Diseases of the Urinary Tract.** STAN at Rickey's Hyatt House, Palo Alto. Thursday-Friday. 16 hrs. $200.

April 9-11—**General Surgery.** UCSF. Thursday-Saturday.

April 23-24—**XII Jules Stein Lecture and Annual Postgraduate Seminar—Anterior Segment Disease: Current Update on Immunology, Corneal Disease, Refractive Surgery, and Contact Lenses.** Jules Stein Eye Institute, Los Angeles. Thursday-Friday. 16 hrs. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024. (213) 825-4617.

April 25—**Radial Keratotomy Workshop.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024. (213) 825-4617.

May 9-16—**Management of the Surgical Patient.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 25 hrs. $295.

May 21-22—**Neurosurgery—11th Annual Postgraduate Course.** UCSF. Thursday-Friday.

OF INTEREST TO ALL PHYSICIANS

January 17—**The Myths and Realities of Genital Herpes: What Patients Need to Know.** UCLA. Saturday. 5 hrs. $25.

January 22-24—**Modern Drug Therapy.** STAN. Thursday-Saturday. 15 hrs. $225.

January 23—**Diagnosis and Treatment of Sleep Disorders Patients.** STAN at Marriott, Santa Clara. Friday. 7 hrs. $35.

January 26-31—**Family Practice Refresher Course.** UCI at Newporter Inn, Newport Beach. One week. 50 hrs. Contact: Cont. Ed. in Health Sciences, UCI Extension, P.O. Box AZ, Irvine 92716. (714) 833-5414.

February 6-12—**Annual Mid-Winter Seminar.** Grossmont Hospital at South Lake Tahoe. One week. 13 hrs. $50. Contact: Grossmont Hospital, CME Committee, P.O. Box 158, La Mesa 92041.

February 11-13—**Neurology for Non-Neurologists.** UCSD at Hilton, San Diego. Wednesday-Friday. 22 hrs. $275.

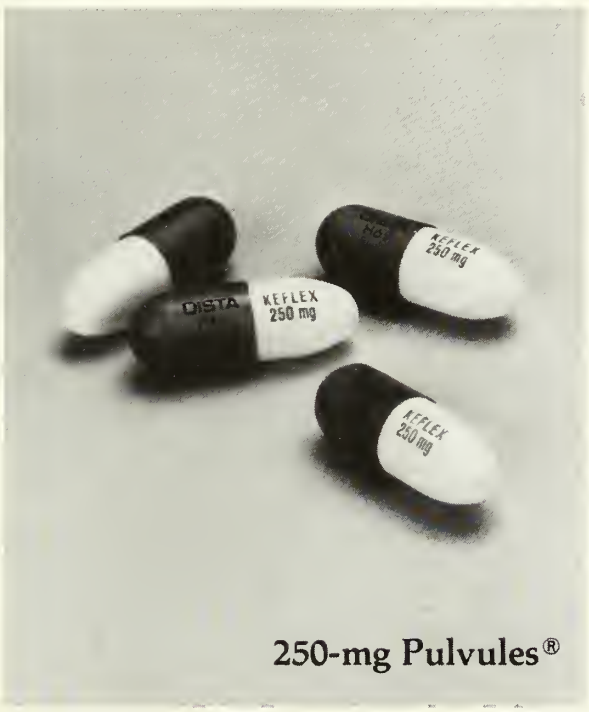
February 11-13—**31st Annual Course for Physicians in Family Practice.** Mt. Zion Hospital and Medical Center, San Francisco. Wednesday-Friday. Contact: Office of Cont. Med. Ed., Mt. Zion Hosp. and Med. Ctr., P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2405.

February 19-22—**Winter Sports Injuries.** UCD at Ahwahnee Hotel, Yosemite. Thursday-Sunday. 14 hrs.

February 20-21—**Pain: New Approaches to Treatment.** Mesa Vista Hospital and Vista Hill Foundation at Hotel del Coronado, Coronado. Friday-Saturday. Contact: Virginia Everett, Vista Hill Fndn., 7798 Starling Dr., San Diego 92123. (714) 278-6761.

(Continued on Page 50)

easy to take



250-mg Pulvules®

Oral Suspension

250 mg/5 ml
100 and 200-ml
sizes

125 mg/5 ml
60, 100, and
200-ml sizes

Pediatric Drops

100 mg/ml
10-ml size

Keflex®
cephalexin

Additional information available
to the profession on request.

DISTA
000823

Dista Products Company
Division of Eli Lilly and Company
Indianapolis, Indiana 46285
Mfd. by Eli Lilly Industries, Inc.
Carolina, Puerto Rico 00630

(Continued from Page 48)

February 23-27—**Basic Science for Clinicians.** STAN. Monday-Friday. 25 hrs. $295.

February 26-27—**Therapeutic Drug Monitoring.** PMC. Thursday-Friday. 12 hrs. $85.

March 1-5—**Medical Evaluation of the Preoperative Patient.** UCD at Ahwahnee Hotel, Yosemite. Sunday-Thursday.

March 3-June 30—**Family Medicine.** USC. Tuesdays; 7:00-10:15 p.m. 56 hrs. $325.

March 5-8—**Critical Care Medicine.** USC at Las Vegas. Thursday-Sunday.

March 5-8—**Sports Medicine.** UCD at Hyatt Lake Tahoe, Incline Village. Thursday-Sunday.

March 6-7—**Advances in Alcoholism—2nd Annual Symposium.** Raleigh Hills Foundation and American Medical Society on Alcoholism at Registry Hotel, Newport Beach. Friday-Saturday. 17 hrs. $150. Contact: Raleigh Hills Fndn., 17861 Cartwright Rd., Irvine 92714. (800) 854-3020 or (714) 641-1616.

March 7-8—**Approaches to Healing.** San Diego County Medical Society and UCSD at San Diego. Saturday-Sunday. 12 hrs. Contact: SDCMS, Medicine and Religion Committee, P.O. Box 23015, San Diego 92123.

March 7-8, 21-22—**Annual Hypnosis Workshop.** San Francisco Academy of Hypnosis at Children's Hospital, San Francisco. Two weekends. 28 hrs. $260. Contact: Jan Brooks, SFAH, 2820 15th Ave., San Francisco 94114.

March 13-15—**Clinical Management.** STAN at The Lodge, Pebble Beach. Friday-Sunday. 8 hrs.

March 13-18—**California Medical Association—110th Annual Session.** Disneyland Hotel, Anaheim. Friday-Wednesday. Contact: Joan Kammerer, CMA.

March 16-20—**Sports Medicine.** University of Hawaii at Princess Kaiulani Hotel, Waikiki, Honolulu. Monday-Friday. 18 hrs. $230. Contact: Joy Lewis, Box CE-CCECS, 2530 Dole St., Honolulu 96822. (808) 948-8244.

March 16-27—**Intensive Residency in Occupational Medicine, Session II.** UCSF. Two weeks.

March 18-20—**Recent Advances in Clinical Nutrition.** UCSD at Vacation Village, San Diego. Wednesday-Friday. 17 hrs.

March 21—**Alcoholism and Its Treatment: 1981.** UCD at Hotel El Rancho Racquet Resort, Sacramento. Saturday. 7½ hrs.

April 8—**Psychiatry for the Non-Psychiatrist.** LLU. Wednesday. 4 hrs. $30.

April 11-12—**Nutrition for the Primary Care Physician.** UCSF. Saturday-Sunday. 14 hrs. $125.

April 11-18—**Office Management of Chronic Pain.** Univ. of Washington School of Medicine at Wailea Beach, Maui. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

April 11-18—**Drug Therapy.** Univ. of Washington School of Medicine at Royal Lahaina, Maui. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

April 12-14—**Family Problems, Aging and Sexuality.** USC. Sunday-Tuesday. 18 hrs. $136.

April 23-25—**Postgraduate Institute.** CMA at Ahwahnee Hotel, Yosemite. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

April 23-26—**Wound Management Workshop.** UCSD at Hilton, San Diego. Thursday-Sunday. 20 hrs.

April 25-26—**Pharmacokinetics '81.** Memorial Hospital Medical Center—UCI Center for Health Education, Long Beach. Saturday-Sunday. Contact: Prog. Coordinator, Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

April 25-May 2—**Diagnostic and Therapeutic Skills.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $350.

May 5-11—**Basic Diving Medicine.** UCSF. One week.

May 11-15—**Postgraduate Institute for Primary Care Physicians—Symposium on Non-Emergency Outpatient Care.** UCSD at Vacation Village, San Diego. Monday-Friday. 27 hrs. $275.

May 16-17—**Eating Disorders.** UCLA. Saturday-Sunday.

May 17-22—**Fingers-to-the-Toes: An Orthopedic Approach for the Family Physician.** UCD at Stanford Sierra Lodge, Fallen Leaf Lake. Sunday-Thursday.

Needs Identification and Fulfillment Tailored to the Individual (NIFTI). UCSF. A new contemporary approach to formal continuing medical education. Participating physicians identify their own CME needs which will be met by a program specifically tailored by UCSF faculty for each individual physician. 25 hrs. minimum; 100, maximum. Fee: $350; $200, UCSF alumni. Contact: Margaret H. Griffith, Extended Programs in Medical Education, 569-U, Univ. of Calif., San Francisco 94143. (415) 666-4251.

Audio-Digest Foundation—A nonprofit subsidiary of CMA. Provides by subscription twice-a-month tape recorded summaries of leading national meetings and authoritative surveys of current literature. A catalog of lectures and panel discussions in all areas of medical practice is also available. Contact: Audio-Digest Foundation, 1577 E. Chevy Chase Dr., Glendale 91206.

Videotape Postgraduate Course for the Primary Care Physician. UCSF, School of Medicine, Div. of Ambulatory and Community Medicine. 24 Category I hrs. upon completion of course as designed—12 programs each year. Contact: Ms. Estelle Nelson, UCSF, Rm. 432-A, 400 Parnassus Ave., San Francisco 94143. (415) 666-1445.

ALASKA, MONTANA and IDAHO

This list of continuing education programs in Alaska, Montana and Idaho is supplied by the University of Washington School of Medicine's program of regional medical education in Washington, Alaska, Montana and Idaho (WAMI). To have events listed, please send information to: WAMI Program, CME Calendar, D-207 Health Sciences Building, School of Medicine, SC-64, University of Washington, Seattle, Washington 98195; or phone (206) 543-6995.

ALASKA

January 28—**Univ. of Wash. Oh/Gyn Sessions** (Anchorage). Wednesday, 12-1 p.m. Providence Hospital. Contact: Hedric Hanson, MD, 3300 Providence Drive, Anchorage, AK 99504. (907) 276-8385.

February 5—**Endorphins—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday, 7:30 pm-9:30 pm. Alaska Psychiatric Institute Medical Library. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99503. (907) 274-7579.

March 19—**Right Brain Functioning—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday, 7:30 pm-9:30 pm. Alaska Psychiatric Institute Medical Library. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99503. (907) 274-7579.

March 25—**Gardnerella Vaginalis Vaginitis—Univ. of Wash. Ob/Gyn Sessions** (Anchorage). Wednesday, 12-1 p.m. Providence Hospital. Contact: Hedric Hanson, MD, 3300 Providence Drive, Anchorage, AK 99504. (907) 276-8385.

April 30—**Group Therapy—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday, 7:30 pm-9:30 pm. Alaska Psychiatric Institute Medical Library. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99503. (907) 274-7579.

May 27—**Univ. of Wash. Ob/Gyn Session** (Anchorage). Wednesday, 12-1 p.m. Providence Hospital. Contact: Hedric Hanson, MD, 3300 Providence Drive, Anchorage, AK 99504. (907) 276-8385.

June 18—**Consultation on Adolescent Problems/Systems Approach—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday, 7:30 pm-9:30 pm. Alaska Psychiatric Institute Medical Library. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99503. (907) 274-7579.

MONTANA

January 21-25—**Sexually Transmitted Diseases—Univ. of Wash. Internal Medicine Review Sessions.**

January 21, Wednesday, Great Falls. 5-7:30 p.m., Columbus Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

January 22, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: D. Frank Johnson, MD, Marillac Hall, Billings, MT 59101. (406) 657-7083.

January 23, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

February 11—**Pediatric Anesthesiology—Univ. of Wash. Pediatrics Sessions** (Great Falls). Wednesday. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

February 18-20—**Adolescent Medicine—Univ. of Wash. Internal Medicine Review Sessions.**

February 18, Wednesday, Great Falls. 5-7:30 p.m. Deaconess Hospital. Contact F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

February 19, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: D. Frank Johnson, MD, Marillac Hall, Billings, MT 59101. (406) 657-7083.

February 20, Friday, Missoula. 8-10:30 a.m. St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

March 5-7—**Montana Section, American College of OB/Gyn Annual Meeting.** Big Sky. Thursday-Saturday. Contact: John T. Browne, MD, 2825 Fort Missoula Rd., Missoula, MT 59801.

March 6-7—**Topics in Internal Medicine.** Big Sky. Friday-Saturday. Contact: D. Frank Johnson, MD, Marillac Hall, Billings, MT 59101. 406) 657-7083.

March 25-27—**New Developments in Cardiology—Univ. of Wash. Internal Medicine Review Sessions.**

March 25, Wednesday, Great Falls. 5-7:30 p.m., Columbus Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

March 26, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: D. Frank Johnson, MD, Marillac Hall, Billings, MT 59101. (406) 657-7083.

March 27, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

April 15—**Pediatric Psychiatry—Univ. of Wash. Pediatrics Sessions** (Great Falls). Wednesday. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

April 22-24—**Congenital Heart Disease in Adults—Univ. of Wash. Internal Medicine Review Sessions.**

April 22, Wednesday, Great Falls. 5-7:30 p.m., Deaconess Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

April 23, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: D. Frank Johnson, MD, Marillac Hall, Billings, MT 59101. (406) 657-7083.

April 24, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

May 27-29—**Office Endocrinology—Univ. of Wash. Internal Medicine Review Sessions.**

May 27, Wednesday, Great Falls. 5-7:30 p.m. Columbus Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

May 28, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: D. Frank Johnson, MD, Marillac Hall, Billings, MT 59101. (406) 657-7083.

May 29, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

June 10—**Allergy—Univ. of Wash. Pediatrics Sessions** (Great Falls). Wednesday. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

IDAHO

January 20—**Endocrinology—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12-1 p.m., St. Anthony Hospital. Contact: David Fischel, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

$25,000,000 LOAN FUND

Available to Physicians

Up to $20,000 Entirely by Mail!

Emphatically private. All transactions through plain, unmarked mail. Use the money for anything. We don't ask.

Attractive rates. Turn-around a few short days.

Call **Ron Malcomb** or send coupon for short-form package. It's brief and easy!

THE BANKERS INVESTMENT COMPANY

(213) 577-3049

99 SOUTH LAKE, SUITE 260
LOCK DRAWER JM-1 • P.O. BOX 4602
PASADENA, CALIFORNIA 91101

MR. R. J. MALCOMB, BANKERS INVESTMENT CO.
LOCK DRAWER JM-1, P.O. BOX 4602
PASADENA, CALIFORNIA 91101

AMOUNT I WANT $ _____

NAME _____

ADDRESS _____

CITY _____ STATE _____

ZIP _____ PHONE _____

February 14-21—**Perinatal Critical Care.** Sun Valley. Saturday-Sunday. Elkhorn Inn. Contact: Univ. of Wash. School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 21-28—**Sports Medicine.** Sun Valley. Saturday-Saturday. Elkhorn Inn. Contact: Univ. of Wash. School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 16—**Gyn Oncology—Univ. of Wash. Ob/Gyn Sessions** (Boise). Monday. 12-1 p.m., St. Luke's Hospital. Contact: David M. Barton, MD, 999 N. Curtis Rd., Boise, ID 83706. (208) 385-9391.

March 17—**Infectious Diseases—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12-1 p.m., St. Anthony Hospital. Contact: David Fischel, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

May 18—**Evaluation and Treatment of Premature Labor—Univ. of Wash. Ob/Gyn Sessions** (Boise). Monday. 12-1 p.m., St. Luke's Hospital. Contact: David M. Barton, MD, 999 N. Curtis Rd., Boise, ID 83706. (208) 385-9391.

May 19—**Psychiatry—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12-1 p.m., St. Anthony Hospital. Contact: David Fischel, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

OREGON

This bulletin of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

University of Oregon Medical School, Department of Psychiatry, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, University of Oregon Medical School. Contact: Dept. of Psychiatry, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8144.

University of Oregon Medical School, Department of Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, University of Oregon Medical School. Contact: Dept. of Medicine, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8607.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, OR 97213. (503) 234-8211.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00-9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee, P.O. Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

EMERGENCY MEDICINE

January 30-31—**American College of Emergency Physicians Winter Conference.** Portland. Friday-Saturday. Jantzen Beach Thunderbird. Contact: Veronica Storey, Oregon ACEP, 5210 SW Corbett Ave, Portland, OR 97201. (503) 226-1555.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center, Portland. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-7590.

February 9-13—**Twelfth Annual Family Practice Review.** Portland. Monday-Friday. Marriott Hotel. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

SURGERY

March 6-7—**Surgery.** Portland. Friday-Saturday. Downtown Red Lion. For additional information please contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, Portland 97201. (503) 225-8700.

INTEREST TO ALL PHYSICIANS

April 2-3—**Current Concepts in Drug Therapy.** Portland. Thursday-Friday. Jantzen Beach Thunderbird. For additional information please contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, Portland 97201. (503) 225-8700.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. Please send information to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle 98121; or phone (206) 623-4801.

January 16-17—**Beta Blocking Agents/Calcium Antagonists.** Seattle. Friday-Saturday. Contact: U/W School of Medicine.

January 23-24—**Pediatric Developmental Diagnosis.** Seattle. Friday-Saturday. Contact U/W School of Medicine.

January 24—**New Approaches to Gastrointestinal Bleeding.** Tacoma. Saturday. St. Joseph Hospital. Contact: CME Pierce County.

January 25-February 1—**Sports Medicine Seminar.** Maui, Hawaii. Sunday-Sunday. Wailea, Maui, Hawaii. Contact: Sports Visions, Central Way Plaza No. 15, Central Way No. 258, Kirkland, WA 98033.

January 26—**Lipids and Diabetes—U/W Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

January 27—**Univ. of Wash. OB/GYN Sessions** (Spokane). Tuesday. 12-1 p.m., Sacred Heart Medical Center. Contact: Wm. Harvey Frazier, MD, West 101 8th Ave., Spokane, WA 99204. (509) 838-8347.

January 29-30—**Financial Planning for Physicians.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

January 31—**The Care of Normal Children.** Seattle. Saturday. Group Health Hospital, 6th Floor Conference Area. Contact: Jackie Kersh, Office of Medical Education, 201 16th Avenue East, A-5, #321, Seattle, WA 98112. (206) 326-7349.

February 2-6—**Ski & Learn 81.** Crystal Mountain. Monday-Friday. Silver Skis Chalet, Crystal Mountain. Contact: Carolyn M. Palmer, 3700 140th Avenue NE, Bellevue, WA 98005. (206) 883-8852.

February 5-6—**Schizophrenia and Depression.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

February 6-7—**Workshops in Fluid and Electrolyte Disorders.** Seattle. Friday-Saturday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

February 10—**Anesthesiology and Pediatrics—Univ. of Wash. Pediatrics Sessions** (Spokane). Tuesday. 12-1 p.m., Sacred Heart Medical Center. Contact: Frank Reynolds, MD, WAMI Office, 3 North, Sacred Heart Medical Center, Spokane, WA 99204. (509) 455-8220.

February 12-14—**National Health Service Corps.** Seattle. Thursday-Saturday. Contact: U/W School of Medicine.

February 14—**Nutrition/Anemia.** Saturday. University of Puget Sound. Tacoma. Contact: CME Pierce County.

February 14-21—**Sports Medicine. Sun Valley,** ID. Saturday-Saturday. U/W at Elkhorn Inn, Sun Valley, ID. Contact: U/W School of Medicine.

February 21-28—**Perinatal Critical Care.** Sun Valley, ID. Saturday-Saturday. U/W at Elkhorn Inn, Sun Valley, ID. Contact: U/W School of Medicine.

February 21-28—**Practical Neurology.** Ilikai, Honolulu, Hawaii. Saturday-Saturday. U/W at Ilikai, Honolulu, Hawaii. Contact: U/W School of Medicine.

February 21-28—**Metabolism and Endocrinology.** Kona, Hawaii. Saturday-Saturday. U/W at Kona Surf, Kona, Hawaii. Contact: U/W School of Medicine.

February 23—**Emergency Medical Services—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD. P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

February 26-27—**Burns: Care & Prevention.** Thursday-Friday. St. Joseph Hospital. Tacoma. Contact: CME Pierce County.

February 27—**Diagnosis and Treatment of Common Arthritic Diseases.** Seattle. Friday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

March 6-7—**Clinical Pharmacology for the Practitioner.** Seattle. Friday-Saturday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

March 6-7—**Trauma.** Friday-Saturday. Tacoma General Hospital. Contact: CME Pierce County.

March 7—**Handicapped Child.** Seattle. Saturday. Contact: U/W School of Medicine.

March 12-13—**Tacoma Academy of Internal Medicine.** Tacoma. Thursday-Friday. Contact: CME Pierce County.

March 16—**Gyn Oncology—Univ. of Wash. OB/GYN Sessions** (Spokane). Tuesday. 12-1 p.m., Sacred Heart Medical Center. Contact: Wm. Harvey Frazier, MD, West 101 8th Ave., Spokane, WA 99204. (509) 838-8347.

March 17—**Epilepsy.** Spokane. Tuesday. Contact: U/W School of Medicine.

March 19-21—**Pediatric Rehabilitation.** Thursday-Saturday. Mary Bridge Childrens' Hospital. Tacoma. Contact: CME Pierce County.

March 23—**Pain—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

March 23-27—**Advances in Family Practice.** Seattle. Monday-Friday. Contact: U/W School of Medicine.

March 27—**Sexually Transmitted Diseases.** Seattle. Friday. Contact: U/W School of Medicine.

March 30-April 10—**Rehabilitation Medicine Review.** Seattle. Monday-Friday. Contact: U/W School of Medicine.

April 3—**Nutrition in the Hospitalized Patient.** Seattle. Friday. Contact: U/W School of Medicine.

April 4—**Mason Clinic Day.** Seattle. Saturday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

April 4-11—**Current Concepts in OB/GYN.** Kona, Hawaii. Saturday-Saturday. U/W at Kona Surf, Kona, Hawaii. Contact: U/W School of Medicine.

April 11-18—**Office Management of Chronic Pain.** Maui, Hawaii. Saturday-Saturday. U/W at Wailea Beach, Wailea, Maui, Hawaii. Contact: U/W School of Medicine.

April 11-18—**Drug Therapy.** Maui, Hawaii. Saturday-Saturday. U/W at Royal Lahaina, Maui, Hawaii. Contact: U/W School of Medicine.

April 14—**Pediatric Psychiatry—Univ. of Wash. Pediatrics Sessions** (Spokane). Tuesday. 12-1 p.m., Sacred Heart Medical Center. Contact: Frank Reynolds, MD, WAMI Office, 3 North, Sacred Heart Medical Center, Spokane, WA 99204. (509) 455-8220.

April 18-25—**Emergency Medical Care.** Maui, Hawaii. Saturday-Saturday. U/W at Wailea Beach, Maui, Hawaii. Contact: U/W School of Medicine.

April 27—**Total Parenteral Nutrition—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

April 30-May 2—**Trauma.** Seattle. Thursday-Saturday. Contact: U/W School of Medicine.

May 1—**Management of Acute Medical Problems.** Seattle. Friday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

May 7-8—**Medical Genetics and Teratology.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

COURSE SPONSORS AND CONTACT INFORMATION

CME PIERCE COUNTY—Contact: Mrs. Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON) — Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Sandra McDonald, Division of Continuing Medical Education, Virginia Mason Medical Center, 1100 Ninth Avenue, Seattle, WA 98101. (206) 223-6898.

May 15-16—**Medical Applications of Real-Time Ultrasound.** Seattle. Friday-Saturday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

May 15—**Medical Alumni.** Seattle. Friday. Contact: U/W School of Medicine.

May 18—**Arrhythmias—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

May 19—**Evaluation and Treatment of Premature Labor—Univ. of Wash. OB/GYN Sessions.** (Spokane). Tuesday. 12-1 p.m., Sacred Heart Medical Center. Contact: Wm. Harvey Frazier, MD, West 101 8th Ave., Spokane, WA 99204. (509) 838-8347.

May 21-22—**Critically Ill Surgical Patient.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

May 23-30—**Allergy and Immunology.** Maui, Hawaii. Saturday-Saturday. U/W at Wailea Beach, Maui, Hawaii. Contact: U/W School of Medicine.

June 4-6—**Radiology Northwest V.** Seattle. Thursday-Saturday. Contact: U/W School of Medicine.

June 4-5—**Pacific Northwest Chapter of the American College of Chest Physicians: Cardiopulmonary Symposium.** Seattle. Thursday-Friday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

June 9—**Pediatric Allergy—Univ. of Wash. Pediatrics Sessions** (Spokane). Tuesday. 12-1 p.m., Sacred Heart Medical Center. Contact: Frank Reynolds, MD, WAMI Office, 3 North, Sacred Heart Medical Center, Spokane, WA 99204. (509) 455-8220.

June 11-12—**Regional Anesthesia and Nerve Block.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

June 15-19—**Death Investigation.** Seattle. Monday-Friday. Contact: U/W School of Medicine.

June 18-19—**Respiratory Care.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

June 18-20—**Modern Office Procedures: Minor Surgeries.** Seattle. Thursday-Saturday. Contact: U/W School of Medicine.

June 22—**Ophthalmology for the Internist—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

July 19-27—**Alaska Cruise: OB/GYN.** Sunday-Monday. Contact: U/W School of Medicine.

July 25-26—**Washington State Society of Anesthesiologists: Seafair III Anesthesia Meeting.** Seattle. Saturday-Sunday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

August 5-7—**Great Debates in Otolaryngology.** Seattle. Wednesday-Friday. Contact: U/W School of Medicine.

August 21-28—**Alaska Cruise: Radiology.** Friday-Friday. Contact: U/W School of Medicine.

August 21-28—**Alaska Cruise: Strabismus.** Friday-Friday. Contact: U/W School of Medicine.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the Academy for Continuing Medical Education, a foundation of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Academy for Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the Academy at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the Academy for current details.

GRAND ROUNDS

SPONSOR: Primary Children's Medical Center
TITLE: **Pediatric Grand Rounds**
LOCATION: PCMC
DATE: First and third Thursdays—8:00 a.m.
CONTACT: Cathy Van Komen (801) 363-1221
SPONSOR: Utah Valley Hospital, Provo
TITLE: **Interdepartmental Grand Rounds**
LOCATION: UVH
CONTACT: Gary Watts, MD (801) 373-7850 (Ext. 2143)

* * *

January 17-21

SPONSOR: Utah Ophthalmological Society/University of Utah/Johnson & Johnson
TITLE: **Interocular Lens Course**
LOCATION: Snowbird
FEE: To be announced
CREDIT: 24 hours
CONTACT: A. Thomas Williams, MD (801) 262-6111

SPONSORS OF COURSES—ABBREVIATIONS

AF: Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.
CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.
CWH: Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461
FHP: Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.
HAFB: Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.
LDSH: Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.
MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.
OEH: Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.
OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409
PCMC: Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.
SHCC: Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.
SLSC: Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.
UAFP: Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.
UUMC: University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.
UVH: Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.
VAMC: Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

January 19
SPONSOR: University of Utah/Mead Johnson
TITLE: **Infant Nutrition—A Foundation for Lasting Health; and Medical Update—Clinical Encounters**
LOCATION: Skaggs Hall, University Medical Center
FEE: To be announced
CREDIT: 3 hours
CONTACT: Gary M. Chan, MD (801) 581-3082

January 24-31
SPONSOR: University of Utah
TITLE: **6th Annual Snowbird Radiology Conference**
LOCATION: Snowbird
FEE: To be announced
CREDIT: 20 hours
CONTACT: P. Ruben Koehler, MD (801) 581-8188

January 31-February 7
SPONSOR: University of California, San Francisco, CA
TITLE: **Infectious Diseases in Clinical Practice**
LOCATION: Park City
FEE: $200.00 ($250.00 after October 15, 1980)
CREDIT: 20 hours
CONTACT: Extended Programs in Medical Education
University of California
1308 3rd Avenue
San Francisco, CA 94143
(415) 666-2483 or 666-2894

February 4
SPONSOR: University of Utah, Dept. of Internal Medicine
TITLE: **Arthritis and Rheumatology**
LOCATION: UUMC, Classroom D, 7-9 pm
FEE: None
CREDIT: 2 hours
CONTACT: Malcolm Berenson, MD (801) 581-7803

February 9-12
SPONSOR: University of Utah
TITLE: **10th Annual Family Practice Refresher Course**
LOCATION: Salt Lake Hilton
FEE: To be announced
CREDIT: 28 hours
CONTACT: David N. Sundwall, MD (801) 581-8633

February 15-20
SPONSOR: University of Utah
TITLE: **Update on Clinical Microbiology and Immunology**
LOCATION: Park City
FEE: To be announced
CREDIT: 24 hours
CONTACT: John M. Matsen, MD (801) 581-5514

February 17-20
SPONSOR: Primary Children's Medical Center
TITLE: **Postgraduate Course in Pediatric Surgery**
LOCATION: Park City
FEE: $250.00
CREDIT: 12 hours
CONTACT: Stan Everett (801) 350-1100

February 20-24
SPONSOR: University of Utah
TITLE: **26th Annual Postgrad Course in Anesthesiology**
LOCATION: Hotel Utah, Salt Lake City
FEE: To be announced
CREDIT: 16 hours
CONTACT: Theodore H. Stanley, MD (801) 581-6393

February 21-24
SPONSOR: University of Utah
TITLE: **22nd Annual OB-BYN Course**
LOCATION: Holiday Inn, Park City
FEE: $250.00
CREDIT: 15 hours
CONTACT: David H. Engelberg, MD (801) 581-7647

February 22-27
SPONSOR: Utah Ophthalmological Society
TITLE: **OUS Winter Meeting**
LOCATION: Park City
FEE: To be announced
CREDIT: 16 hours
CONTACT: A. Thomas Williams, MD (801) 268-6111

February 25-27
SPONSOR: University of Utah/Intermountain Pediatric Society/ American Academy of Pediatrics
TITLE: **Common Problems in Pediatrics III**
LOCATION: Salt Lake Hilton
FEE: $150.00+$15.00 each mini-course
CREDIT: 16 hours
CONTACT: Bruce Buehler, MD (801) 581-7877

February 25-28
SPONSOR: University of Utah
TITLE: **Gynecologic Oncology Course**
LOCATION: To be announced
FEE: To be announced
CREDIT: 15 hours
CONTACT: David H. Engleberg (801) 581-5501

February 27-28
SPONSOR: LDS Hospital/Dixie Medical Center
TITLE: **Second Annual Dixie Medical Center Symposium**
LOCATION: Hilton Inn, St. George
FEE: To be announced
CREDIT: To be announced
CONTACT: Carlyle F. Stout, MD (801) 673-4642
Warren Stucki, MD (801) 628-1641

February 25-March 7
SPONSOR: University of Utah
TITLE: **Midwinter Radiology Pacific Cruise Meeting**
LOCATION: Departs from Los Angeles
FEE: $300.00
CREDIT: To be announced
CONTACT: P. Ruben Koehler, MD (801) 581-8818

February 28-March 7
SPONSOR: University of Utah
TITLE: **6th Annual Advances in Internal Medicine**
LOCATION: Snowbird
FEE: $225.00
CREDIT: 25 hours
CONTACT: Malcolm Berenson, MD (801) 581-7802

February 28-March 7
SPONSOR: University of Utah
TITLE: **Nutrition and Contemporary Medicine**
LOCATION: Park City
FEE: $200.00
CREDIT: 25 hours
CONTACT: Malcolm Berenson, MD (801) 581-7802

March 6
SPONSOR: University of Utah, Dept. of Internal Medicine
TITLE: **Infectious Disease**
LOCATION: UUMC
FEE: None
CREDIT: 2 hours
CONTACT: Malcolm Berenson, MD (801) 581-7803

March 7-14
SPONSOR: University of Utah
TITLE: **Medical and Surgical Advances in Gastroenterology**
LOCATION: Snowbird
FEE: To be announced
CREDIT: 25 hours
CONTACT: Malcolm Berenson, MD (801) 581-7802

WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—4107 Laurel St., Anchorage 99504. Annual Meeting: May 23-27, 1981, Glacier Bay Lodge, Glacier Bay.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. Annual Meeting: April 22-26, 1981, The Pointe Resort, Phoenix.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: March 13-18, 1981, Disneyland Hotel, Anaheim.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. Annual Meeting: September 9-12, 1981, Keystone.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. Annual Meeting: October 12-16, 1981, Ilikai Hotel, Honolulu.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. Annual Meeting: July 23-26, 1981, Sun Valley.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Interim Meeting: April 10-11, 1981, Colonial Inn, Helena. Annual Meeting: October 1-3, 1981, Copper King Inn, Butte.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. Annual Meeting: May 15-17, 1981, Carson City.

New Mexico Medical Society—2650 Yale SE, Albuquerque 87106. Annual Meeting: May 6-8, 1981, Hilton Inn, Albuquerque.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. Annual Scientific Session: October 29-30, 1981, Portland.

Utah State Medical Association—540 East Fifth South St., Salt Lake City 84102. Annual Meeting: September 8-11, 1981, Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. Annual Meeting: September 24-27, 1981, Davenport Hotel, Spokane.

Wyoming State Medical Society—P.O. Drawer 4009, Cheyenne 82001. Annual Meeting: June 22-26, 1981, Ramada Snow King Inn, Jackson.

March 14-21

SPONSOR: University of Utah
TITLE: **3rd Annual Park City Radiology Conference: Neuroradiology**
LOCATION: Park City
FEE: $240.00
CREDIT: To be announced
CONTACT: P. Ruben Koehler, MD (801) 581-8818

April 1

SPONSOR: University of Utah, Dept. of Internal Medicine
TITLE: **Clinical Pharmacology**
LOCATION: UUMC
FEE: None
CREDIT: 2 hours
CONTACT: Malcolm Berenson, MD (801) 581-7803

April 8-10

SPONSOR: University of Utah Rocky Mountain Center for Occupational and Environmental Health/ University of Arizona Center for Occupational Safety and Health/University of Texas Health Science Center, School of Public Health
TITLE: **3rd Annual Park City Environmental Health Conference: Legal and Ethical Dilemmas in Occupational Health**
LOCATION: Prospector Square Lodge, Park City
FEE: To be announced
CREDIT: To be announced
CONTACT: Katharine Blosch (801) 581-5710

April 17

SPONSOR: Academy for Continuing Medical Education
TITLE: **First Intermountain Conference on CME**
LOCATION: TriArc Travel Lodge, Salt Lake City
FEE: $50.00 (attendance limited to 100)
CREDIT: 7 hours (certified by University of Utah College of Medicine)
CONTACT: Pam Hanson, ACME (801) 355-5290

June 22-25

SPONSOR: University of Utah
TITLE: **Alcoholism and Other Drug Dependencies**
LOCATION: University Medical Center, Classroom C
FEE: To be announced
CREDIT: 28 hours
CONTACT: James R. Swenson, MD (801) 581-7985

Note: Dates, times, places and programs are subject to change on occasion. Please check with the sponsoring organization or the Academy for details.

Index to
The Western Journal of Medicine Advertising

ARTHRITIS FOUNDATION 9
AYERST LABORATORIES
Premarin 22, 23, 24
BANKERS INVESTMENT COMPANY/SECURITY PACIFIC FINANCE CORP. 51
BRIGGS COMPUTERS AND SOFTWARE 5
BRISTOL LABORATORIES
Tegopen 34, 35, 36
BURROUGHS WELLCOME CO.
Empirin c Codeine 6
Neosporin Topical 29
CLASSIFIED 38, 40, 42, 43
CME VIDEO CLINICS 39
DOCTORS' CO., THE 41
ELI LILLY AND COMPANY
Keflex 49
HEALTH FACILITIES DEVELOPMENT INC. 16
HELIOSYSTEMS 47
KIDNEY FOUNDATION OF SOUTHERN CALIFORNIA 36
NORCAL MUTUAL INSURANCE COMPANY 15
NORTHRIDGE HOSPITAL FOUNDATION
Oncology Update 1981 37
PERALTA HOSPITAL-EDUCATION & TRAINING PROGRAM
Regional Sleep Disorder Program 20
ROCHE LABORATORIES
Bactrim ..... 2nd Cover, 1, 2
Limbitrol 26, 27, 28
Trimpex 18, 19, 20
Corporate 33
Valium ..... 3rd and 4th Cover
SMITH, KLINE & FRENCH CO.
Dyazide 3
E. R. SQUIBB & SONS INC.
Corgard 11, 12, 13, 14
WESTERN JOURNAL OF MEDICINE, THE
Subscription 44
WESTERN SOCIETY OF ALLERGY & IMMUNOLOGY
20th Annual Scientific Session 20
WYETH LABORATORIES
Ativan 16, 17
Lo/Ovral 30, 31, 32

THE FRANCIS A. COUNTWAY LIBRARY OF MEDICINE BOSTON JUN 9 1981

THE WESTERN Journal of Medicine

VOLUME 134 • NUMBER 2 **FEBRUARY 1981**

97 *Amygdalin Toxicity Studies in Rats Predict Chronic Cyanide Poisoning in Humans*
GEORGE W. NEWTON, MA; ERIC S. SCHMIDT, BS; JERRY P. LEWIS, MD; ERIC CONN, PhD, and RUTH LAWRENCE, MD

104 *Breast Reconstruction for Premalignant and Malignant Disease—An Update*
DAVID B. APFELBERG, MD; BART MALDOWNEY, MD; DONALD R. LAUB, MD; MORTON R. MASER, MD, and HARVEY LASH, DDS, MD

MEDICAL PROGRESS

109 *Disorders of Platelet Function—Mechanisms, Diagnosis and Management*
LOTHAR B. HUEBSCH, MD, and LAURENCE A. HARKER, MD

SPECIALTY CONFERENCE

128 *The Use of Fibrinolytic Agents* Moderator: STANLEY I. SCHRIER, MD
Participants: ARTHUR A. SASAHARA, MD; ROBERT T. WALL, MD, and CHRISTINA B. HARBURY, MD

MEDICAL STAFF CONFERENCE

134 *Seronegative Spondylarthritis* Chief Discussant: DAVID WOFSY, MD

IMPORTANT ADVANCES IN CLINICAL MEDICINE

141 *Psychiatry—Epitomes of Progress*

EDITORIALS

147 • *Hopes and No Hopes for the Next Quadrennium* • *Platelets in Perspective* • *Has the Public's Interest in Health Care Peaked?* • *Why Thrombolytic Therapy*

CASE REPORTS

153 *Immunoglobulin D Myeloma—Report of a Case With Unusual Neurological Complications*
VINCENT CAGGIANO, MD; SURL L. NIELSEN, MD; FRANK J. GLASSY, MD, and DAVID F. DOZIER, Jr, MD

158 *Human Pulmonary Dirofilariasis in the West* FLAVIO CIFERRI, MD, MPH

162 *Severe Lactic Acidosis and Hypothermia* BRIAN J. MURRAY, MD

CORRESPONDENCE

167 • *Treatment for Heatstroke Victims* • *Tonsillectomy and Adenoidectomy* • *Radiation Therapy for Skin Cancer* • *Possible Hazards of Nylon Athletic Shorts* • *TdT Negative T-ALL* • *The Importance of Making Precise Medical Records in the 1980's* • *Subacute Laetrile Intoxication* • *Private Enterprise Physicians, An Endangered Species?* • *High Altitude Flatus Expulsion (HAFE)* • *Medicaid and the Medical Profession*

SPECIAL ARTICLE

175 *Physician Attitudes Toward Distressed Colleagues* JOHN N. CHAPPEL, MD

HEALTH CARE DELIVERY

181 *Care of Mildly Ill Children Enrolled in Day-care Centers—Management by Parents and by Trained Home Workers*
ALBERT CHANG, MD, MPH; GEORGE KELSO, MD, MPH; MARCIA HARRIS, RN, and ALICE JORDAN, BA

INFORMATION

186 *The Aging Heart—Observations in Patients 40 Years Old and Older*
RICHARD S. COSBY, MD; MARY MAYO, BA; ADRIAN MIREA, BS, and JAMES A. PETERSON, PhD

190 *Book Reviews*

191 *In Memoriam*

Detailed Table of Contents, See Advertising Pages 7 and 8

Information for Authors, See January Issue, Advertising Page 10

★ **CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA, HAWAII AND NEVADA; ALASKA, MONTANA AND IDAHO; OREGON; WASHINGTON; UTAH**
(See Advertising Page 18)

★★ **Official Journal of the California Medical Association, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association and the Washington State Medical Association**

CONSIDER THE COMPARATIVE EFFICACY OF DALMANE® VS. (flurazepam HCl/Roche) OTHER SLEEP MEDICATIONS

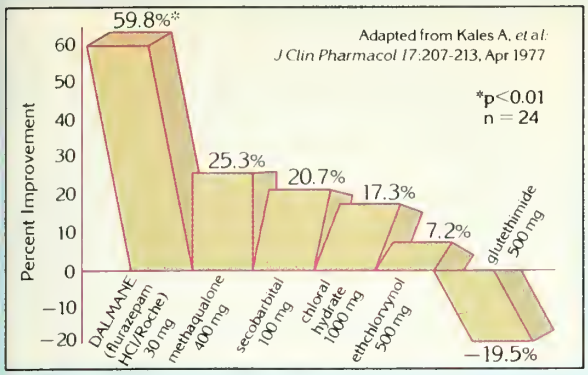
Sleep research laboratory studies show Dalmane (flurazepam HCl/Roche) **more effective for more nights than other sleep medications tested**

Polygraphic appraisal of sleep in 36 insomniac subjects over 14 consecutive nights, proved that of the 9 medications* tested, only Dalmane remained significantly effective for the duration of the study.[1]

While it is reassuring that efficacy can be maintained for this period of time if needed, pharmacological treatment of insomnia should be initiated with the lowest effective dose and continued only as long as judged appropriate to achieve a therapeutic goal. Patients who ingest alcoholic beverages or other CNS depressants should be advised against doing so while on sleep medicatio

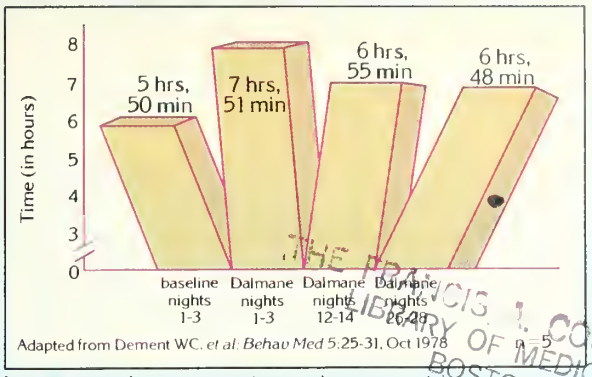
*The drugs studied included 7 commercially available and 2 investigational hypnotics.

Percent decrease in total wake time after 12-14 nights of administration: a comparison of 6 sleep medications.



Percent improvement shown represents mean reductions, in minutes, of insomnia in the parameter of total wake time.

Dalmane (flurazepam HCl/Roche) improved sleep during entire course of therapy.



Improvement shown represents mean improvement, in hours, of total sleep time.

THE FRANCIS A. COUNTWAY LIBRARY OF MEDICINE BOSTON JUN 9 1981

Additional studies showed that Dalmane (flurazepam HCl/Roche) continued to provide effective insomnia relief for 28 consecutive nights of use

Two sleep research laboratory studies with a total of 10 insomniacs investigated for 280 subject nights, conducted at geographically separated university medical centers, proved the longer-term usefulness of Dalmane.[2,3]

Careful assessment of the patient's medical profile should be made. Blood counts and liver and kidney function tests should be done periodically. Patients should be cautioned against engaging in hazardous occupations requiring mental alertness, such as operating machinery or driving a motor vehicle shortly after ingesting the drug.

Plus, efficacy proved in elderly insomniacs with the 15-mg dosage *h.s.*

Six female insomniac patients, aged 67 to 82 years, averaged 1 hour and 23 minutes more sleep nightly during treatment with Dalmane for a period of one week.[4] It should be kept in mind that sleep medication may not always be appropriate for elderly individuals who complain of insomnia. Contributing factors may include requirements for less sleep than in younger years or the establishment of poor sleeping habits.

REFERENCES:
1. Kales A, *et al: J Clin Pharmacol* 17:207-213, Apr 1977
2. Dement WC, *et al: Behav Med* 5:25-31, Oct 1978
3. Kales A, *et al: Clin Pharmacol Ther* 19:576-583, May 1976
4. Frost JD Jr, De Lucchi MR: *J Am Geriatr Soc* 27:541-546, Dec 1979

Sleep within 17 minutes, on average

Sleep with fewer nighttime awakenings

Sleep for 7 to 8 hours, on average

Sleep that does not worsen beyond baseline levels upon discontinuation of medication[1]

DALMANE® (IV)

flurazepam HCl/Roche

15-mg and 30-mg capsules

ROCHE®

Please turn page for a summary of product information.

DALMANE® C-IV
flurazepam HCl/Roche

One 15-mg capsule *h.s.*—usual recommended dosage for elderly or debilitated patients.
One 30-mg capsule *h.s.*—usual adult dosage
(15 mg may suffice in some patients).

Please consult complete product information, a summary of which follows:
Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; in acute or chronic medical situations requiring restful sleep. Objective sleep laboratory data have shown effectiveness for at least 28 consecutive nights of administration. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended.
Contraindications: Known hypersensitivity to flurazepam HCl.
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

Usage in Pregnancy: **Several studies of minor tranquilizers (chlordiazepoxide, diazepam, and meprobamate) suggest increased risk of congenital malformations during the first trimester of pregnancy. Dalmane, a benzodiazepine, has not been studied adequately to determine whether it may be associated with such an increased risk. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.
Precautions: In elderly and debilitated patients, it is recommended that the dosage be limited to 15 mg to reduce risk of oversedation, dizziness, confusion and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies, or with impaired renal or hepatic function. Periodic blood counts and liver and kidney function tests are advised during repeated therapy.
Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, paradoxical reactions, e.g., excitement, stimulation and hyperactivity, and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase.
Dosage: Individualize for maximum beneficial effect.
Adults: 30 mg usual dosage; 15 mg may suffice in some patients.
Elderly or debilitated patients: 15 mg recommended initially until response is determined.
Supplied: Capsules containing 15 mg or 30 mg flurazepam HCl.

ROCHE®
ROCHE PRODUCTS INC.
Manati, Puerto Rico 00701

Two convenient dosage forms: 100 mg (white) and 300 mg (peach) Scored Tablets

Tablets imprinted with brand name to assist in tablet identification.

Wellcome
Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

THE WESTERN Journal of Medicine

CLASSIFIED RATES

$4.00 PER LINE

(Average six words per line)

FIVE LINE MINIMUM
BOX NUMBERS $2.00 EXTRA

• • •

DISPLAY CLASSIFIED

$40 PER COLUMN INCH

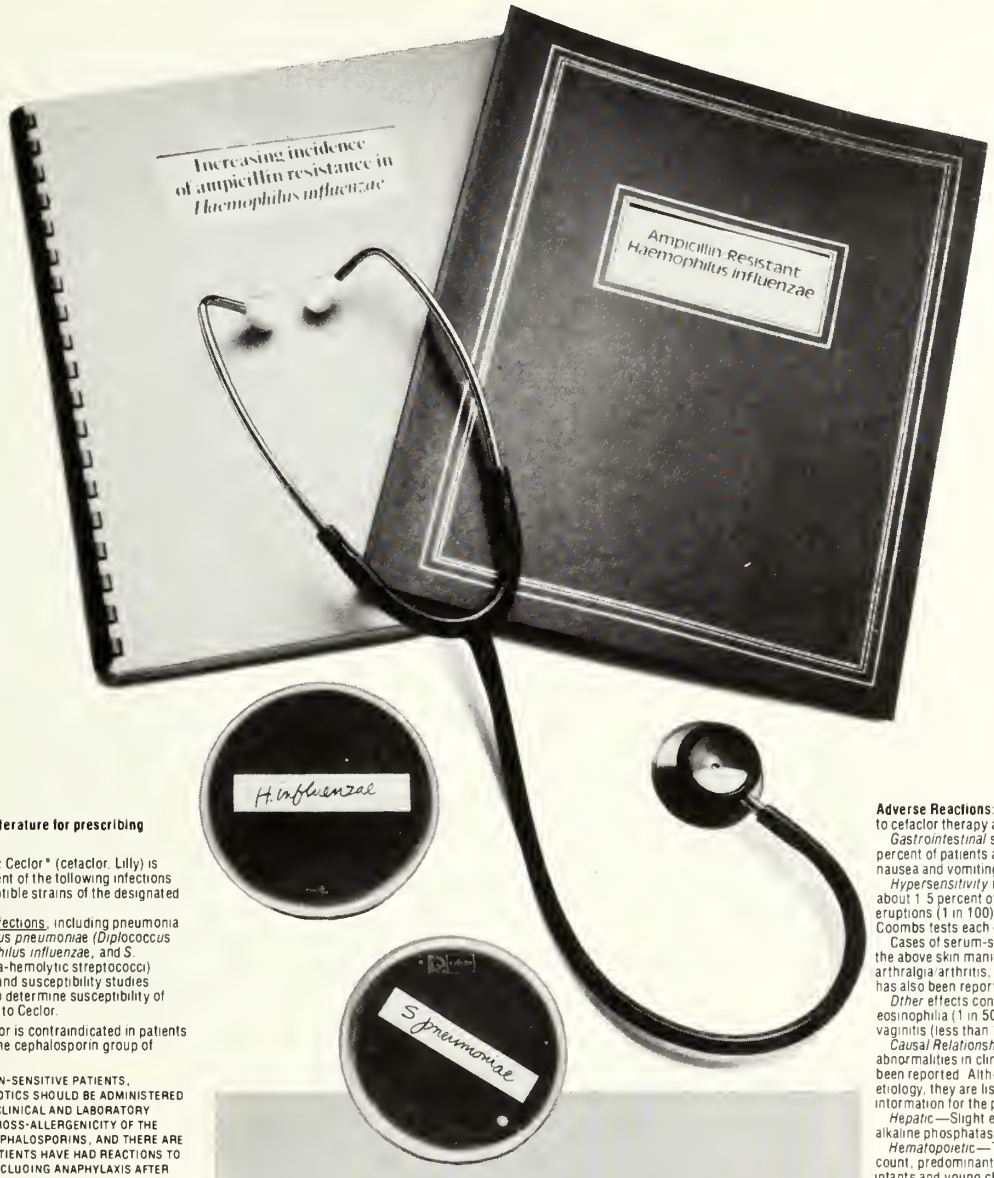
Three column page rate available on request

COLUMN WIDTH
1 column 2⅛" • 2 columns 4½" • 3 columns 7"
(Classified Advertising is payable in advance)
Please type or print advertising copy

DEADLINE
1st of Month before publication date

731 MARKET STREET
SAN FRANCISCO, CA 94103 • (415) 777-2000

An added complication... in the treatment of bacterial bronchitis*



Some ampicillin-resistant strains of Haemophilus influenzae—a recognized complication of bacterial bronchitis*—are sensitive to treatment with Ceclor.[1-6]

In clinical trials, patients with bacterial bronchitis due to susceptible strains of Streptococcus pneumoniae, H. influenzae, S. pyogenes (group A beta-hemolytic streptococci), or multiple organisms achieved a satisfactory clinical response with Ceclor.[7]

Ceclor®
cefaclor

Pulvules®, 250 and 500 mg

Brief Summary
Consult the package literature for prescribing information.

Indications and Usage: Ceclor® (cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

Lower respiratory infections, including pneumonia caused by *Streptococcus pneumoniae (Diplococcus pneumoniae), Haemophilus influenzae*, and *S. pyogenes* (group A beta-hemolytic streptococci)

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor.

Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS TO BOTH DRUG CLASSES (INCLUDING ANAPHYLAXIS AFTER PARENTERAL USE).

Antibiotics, including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

Precautions: If an allergic reaction to cefaclor occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids.

Prolonged use of cefaclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs test may be due to the drug.

Ceclor should be administered with caution in the presence of markedly impaired renal function. Under such a condition, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

As a result of administration of Ceclor, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly).

Usage in Pregnancy—Although no teratogenic or antifertility effects were seen in reproduction studies in mice and rats receiving up to 12 times the maximum human dose or in ferrets given three times the maximum human dose, the safety of this drug for use in human pregnancy has not been established. The benefits of the drug in pregnant women should be weighed against a possible risk to the fetus.

Usage in Infancy—Safety of this product for use in infants less than one month of age has not been established.

Adverse Reactions: Adverse effects considered related to cefaclor therapy are uncommon and are listed below:

Gastrointestinal symptoms occur in about 2.5 percent of patients and include diarrhea (1 in 70) and nausea and vomiting (1 in 90).

Hypersensitivity reactions have been reported in about 1.5 percent of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs tests each occur in less than 1 in 200 patients.

Cases of serum-sickness-like reactions, including the above skin manifestations, fever, and arthralgia/arthritis, have been reported. Anaphylaxis has also been reported.

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients).

Causal Relationship Uncertain—Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician.

Hepatic—Slight elevations in SGOT, SGPT, or alkaline phosphatase values (1 in 40).

Hematopoietic—Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40).

Renal—Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200). [103080R]

*Many authorities attribute acute infectious exacerbation of chronic bronchitis to either *S. pneumoniae* or *H. influenzae*.[8]

Note: Ceclor® (cefaclor) is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

References

1. Antimicrob. Agents Chemother., *8*: 91, 1975
2. Antimicrob. Agents Chemother., *11*: 470, 1977
3. Antimicrob. Agents Chemother., *13*: 584, 1978
4. Antimicrob. Agents Chemother., *12*: 490, 1977.
5. Current Chemotherapy (edited by W. Siegenthaler and R. Luthy), II: 880. Washington, D.C.: American Society for Microbiology, 1978
6. Antimicrob. Agents Chemother., *13*: 861, 1978
7. Data on file, Eli Lilly and Company.
8. Principles and Practice of Infectious Diseases (edited by G.L. Mandell, R.G. Douglas, Jr., and J.E. Bennett), p. 487. New York: John Wiley & Sons, 1979

Additional information available to the profession on request from Eli Lilly and Company, Indianapolis, Indiana 46285

Eli Lilly Industries, Inc.
Carolina, Puerto Rico 00630

100061

THE WESTERN Journal of Medicine

Since 1902 (ISSN 0093-0415)

731 MARKET ST. • SAN FRANCISCO, CA 94103 • TELEPHONE (415) 777-2000

Official Journal of the California Medical Association, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association and the Washington State Medical Association

Editorial Board

Chairman of the Board
Malcolm S. M. Watts, San Francisco, Ca

Special Editor for Idaho
E. R. W. Fox, Coeur d'Alene, Id

Special Editor for Nevada
Thomas J. Scully, Reno, Nv

Special Editor for Utah
John H. Holbrook, Salt Lake City, Ut

Special Editor for Washington
David Hopkins, Federal Way, Wa

Allergy
Harold S. Novey, Orange, Ca
Abba I. Terr, San Francisco, Ca

Anesthesiology
Ronald L. Katz, Los Angeles, Ca

Cardiac and Thoracic Surgery
John E. Connolly, Irvine, Ca
Albert Starr, Portland, Or

Chest Diseases
Roger K. Larson, Fresno, Ca
Thomas L. Petty, Denver, Co

Dermatology
John H. Epstein, San Francisco, Ca
George F. Odland, Seattle, Wa
Richard B. Stoughton, San Diego, Ca

General and Family Practice
Daniel D. Roberts, Central Point, Or
Harmon E. Holverson, Emmett, Id
Wilfred Snodgrass, Santa Monica, Ca

General Surgery
Fred M. Anderson, Reno, Nv
Daniel T. Cloud, Phoenix, Az
Paul A. Ebert, San Francisco, Ca
Lucius D. Hill, Seattle, Wa
Frank G. Moody, Salt Lake City, Ut

Industrial Medicine and Toxicology
Thomas H. Milby, Berkeley, Ca

Internal Medicine
Robert W. Burrough, Spokane, Wa
Theodore C. Eickhoff, Denver Co
Robert L. Hare, Portland, Or
Robert H. Moser, Philadelphia, Pa
George A. Porter, Portland, Or
Helen M. Ranney, San Diego, Ca
David D. Ulmer, Los Angeles, Ca
Edgar Wayburn, San Francisco, Ca
Ralph C. Williams, Jr., Albuquerque, NM

Neurology
Pierre M. Dreyfus, Sacramento, Ca
Philip D. Swanson, Seattle, Wa
W. C. Wiederholt, La Jolla, Ca

Neurosurgery
John R. Green, Phoenix, Az
Arthur A. Ward, Jr., Seattle, Wa
Charles B. Wilson, San Francisco, Ca

Nuclear Medicine
Joseph P. Kriss, Stanford, Ca

Obstetrics and Gynecology
Ralph C. Benson, Portland, Or
Ralph W. Hale, Honolulu, Hi
W. LeRoy Heinrichs, Stanford, Ca
Morton A. Stenchever, Seattle, Wa

Ophthalmology
Robert S. Hepler, Los Angeles, Ca
Bruce E. Spivey, San Francisco, Ca

Orthopedics
Ernest M. Burgess, Seattle, Wa
Duane M. Kline, Jr., Cheyene, Wy

Otolaryngology
Roger Boles, San Francisco, Ca
Mansfield F. W. Smith, San Jose, Ca

Pathology
Richard L. Kempson, Stanford, Ca

Pediatrics
Louis K. Diamond, San Francisco, Ca
William L. Nyhan, San Diego, Ca
Irving Schulman, Stanford, Ca
Arnold L. Smith, Seattle, Wa

Pharmacology
George N. Aagaard, Seattle, Wa

Physical Medicine and Rehabilitation
Glenn G. Reynolds, San Jose, Ca

Plastic Surgery
Richard P. Jobe, Los Altos, Ca
N. John Wilde, Fresno, Ca

Psychiatry
Carl Eisdorfer, Seattle, Wa
Alan I. Levenson, Tucson, Az
Helen Tausend, Beverly Hills, Ca
Joe Paul Tupin, Sacramento, Ca

Public Health
J. M. Stubblebine, Greenbrae, Ca
Irma M. West, Sacramento, Ca

Radiology
M. Paul Capp, Tucson, Az
Melvin M. Figley, Seattle, Wa
Marshall Rowen, Orange, Ca

Urology
Richard Middleton, Salt Lake City Ut
Thomas A. Stamey, Stanford Ca

Consulting Editor
Medical Services and Health Care
Paul J. Sanazaro, Berkeley, Ca

MALCOLM S. M. WATTS, MD, *Editor*
LLOYD H. SMITH, JR., MD, *Associate Editor*
DAVID GREER, *Managing Editor*
BARBARA T. ROONEY, *Assistant Managing Editor*

editorial communications to:
MALCOLM S. M. WATTS, MD, *Editor*

business communications to:
DAVID GREER, *Managing Editor*

MARY KAY COWANS
Advertising Production Manager

Policy Committee—Editorial Board

JOSEPH F. BOYLE ..... Los Angeles
BRAD COHN ..... San Francisco
GLADDEN V. ELLIOTT ..... La Mesa
SAMUEL HOROWITZ ..... Los Angeles
ROBERT D. BURNETT ..... Sunnyvale
THEODORE W. LORING ..... Eureka
MALCOLM S. M. WATTS ..... San Francisco

Advertisements—THE WESTERN JOURNAL OF MEDICINE is published the first week of each month. Advertising copy must be received not later than the first of the month preceding issue. Advertising rates will be sent on request. Acceptance of advertising is contingent upon approval by the Advertising Committee. The journal reserves the right to reject any advertisement.

ADVERTISING SALES REPRESENTATIVES:

EAST:
SAUL HORNIK
P.O. BOX 246
MORGANVILLE, NJ 07751
TEL: (201) 462-8004

MIDWEST:
R. C. JOHNSON & ASSOCIATES
RICHARD C. JOHNSON
547 WEST MELROSE
CHICAGO, IL 60657
TEL: (312) 327-6969

WEST:
MEDIA SERVICES
DARIEN DELORENZO
LYNNE JEFFES
2612 BELMONT CANYON RD.
BELMONT, CA 94002
TEL. (415) 595-2203
(415) 348-7478

CLASSIFIED:
731 MARKET ST.
SAN FRANCISCO, CA 94103
TEL. (415) 777-2000
(415) 777-0424

Copyright 1980 by the California Medical Association

Owned and Published by the California Medical Association

All material subject to this copyright appearing in THE WESTERN JOURNAL OF MEDICINE may be photocopied for the noncommercial purpose of scientific or educational advancement. Volumes begin with the first of January and the first of July.

The subscription price per year is $10 in the United States and Canada; $18 in all other countries. Single copies are $2. Address all subscription communications to THE WESTERN JOURNAL OF MEDICINE Circulation, 731 Market St., San Francisco, CA 94103.

Allow six weeks for subscriptions to begin. Past issues must be bought individually. So long as reserve stocks are available, missing issue requests from subscribers are honored for up to six months after the issue date. Thereafter, the single copy rate of $2.00 is applicable for each issue available.

"Change of Address"—Requests for change of address should give both the old and new addresses. Allow six weeks for change-over.

CONTRIBUTIONS OF SCIENTIFIC AND ORIGINAL ARTICLES

Responsibilities for Statements and Conclusions in Original Articles—Authors are responsible for all statements, conclusions and methods of presenting their subjects. These may or may not be in harmony with the views of the editorial staff. It is aimed to permit authors to have as wide latitude as the general policy of the journal and the demands on its space may permit. The right to reduce, revise or reject any manuscript is always reserved.

Exclusive Publication—Articles are accepted for publication on condition that they are contributed solely to this journal. Ordinarily contributors will be notified within 60 days if a manuscript is accepted for publication. Every effort will be made to return unused manuscripts.

Length of Articles—Ordinarily articles should not exceed 3,000 words (approximately five printed pages). Under exceptional circumstances only will articles of over 4,000 words be published.

Manuscripts—Manuscripts should be typewritten and double-spaced, and the *original* typescript plus two copies should be submitted.

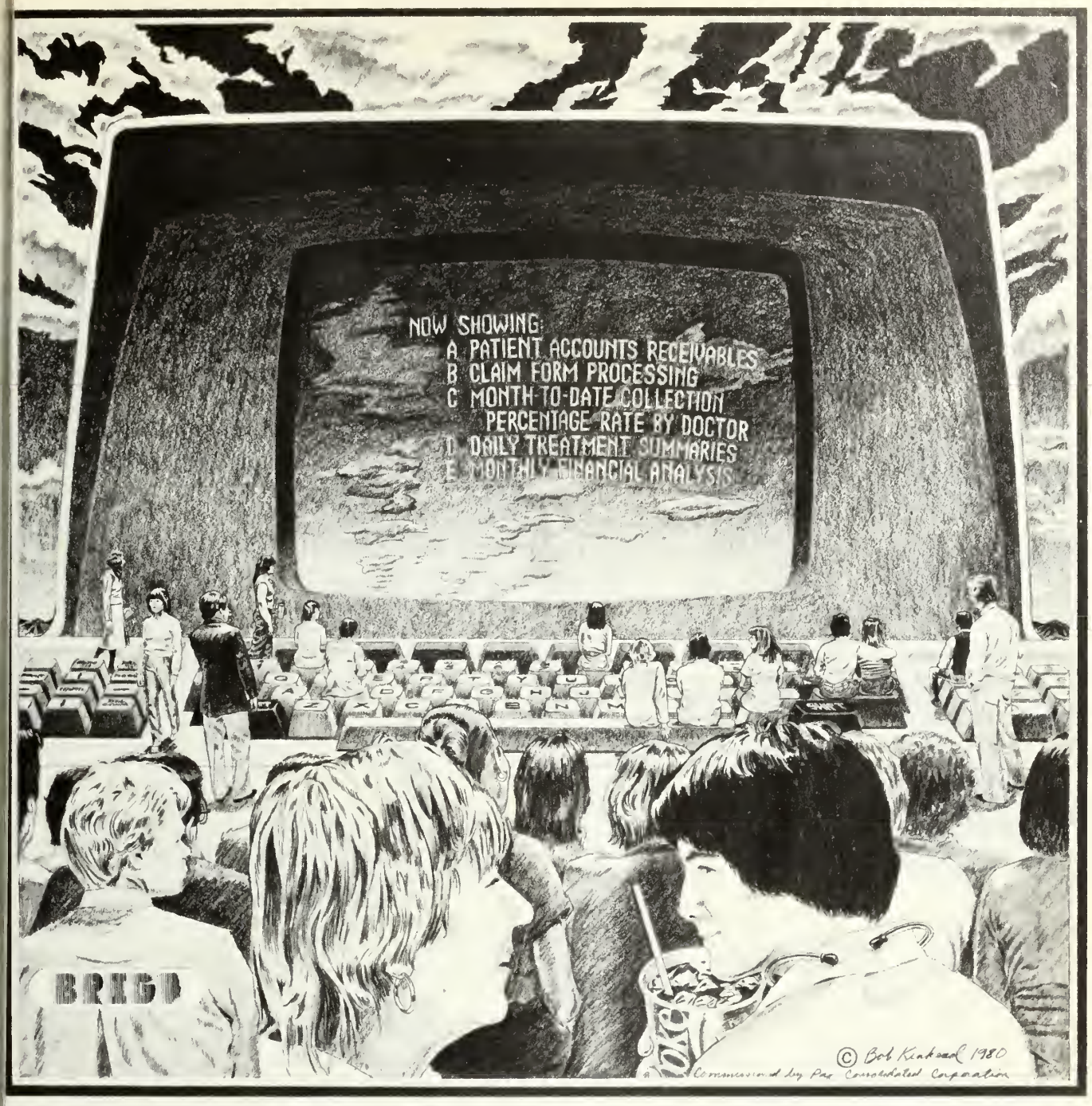
Illustrations—Ordinarily publication of two or three illustrations accompanying an article will be paid for by THE WESTERN JOURNAL OF MEDICINE. Any number beyond this may have to be paid for by the author.

References—References should conform to the following order: name of author, title of article, name of periodical, and volume with inclusive pages, month and year—i.e., Lee GS: The heart rhythm following therapy with digitalis—In theory and practice. Arch Int Med 44:554-562, Dec 1942. They should be listed in the order in which they are cited in the text, numbered in sequence and punctuated as above.

Reprints—Reprints must be paid for by the author at established standard rates.

"Information for Authors" Available on request or see January 1981 issue, advertising page 10.

"Entered as second class matter at the post office in San Francisco under the Act of March 3, 1879." Acceptable for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized August 10, 1918. Publication Number 084480.



Tomorrow's Big Picture.

Today. All of the information you need to operate an efficient, profitable practice comprises the Big Picture.

Daily and monthly financial analysis; summaries by diagnosis, by transaction and by doctor are available at the touch of a finger. And personal statement messages are part of the program.

There's more. Automatic aging. Past due notices. Month-to-date and year-to-date accounts receivable data with collection rate by doctor. Your Brig Office Management System will process claim forms and statements at a rate of three hundred per hour.

Better still, *your* people can learn to operate the system in a few minutes. For less than the cost of an outside billing service. We have leasing, purchase and rental plans.

Make the necessary decision to automate your office. Call us today for a personal demonstration.

BRIGD

COMPUTERS & SOFTWARE

5830 Uplander Way, Culver City, CA 90230

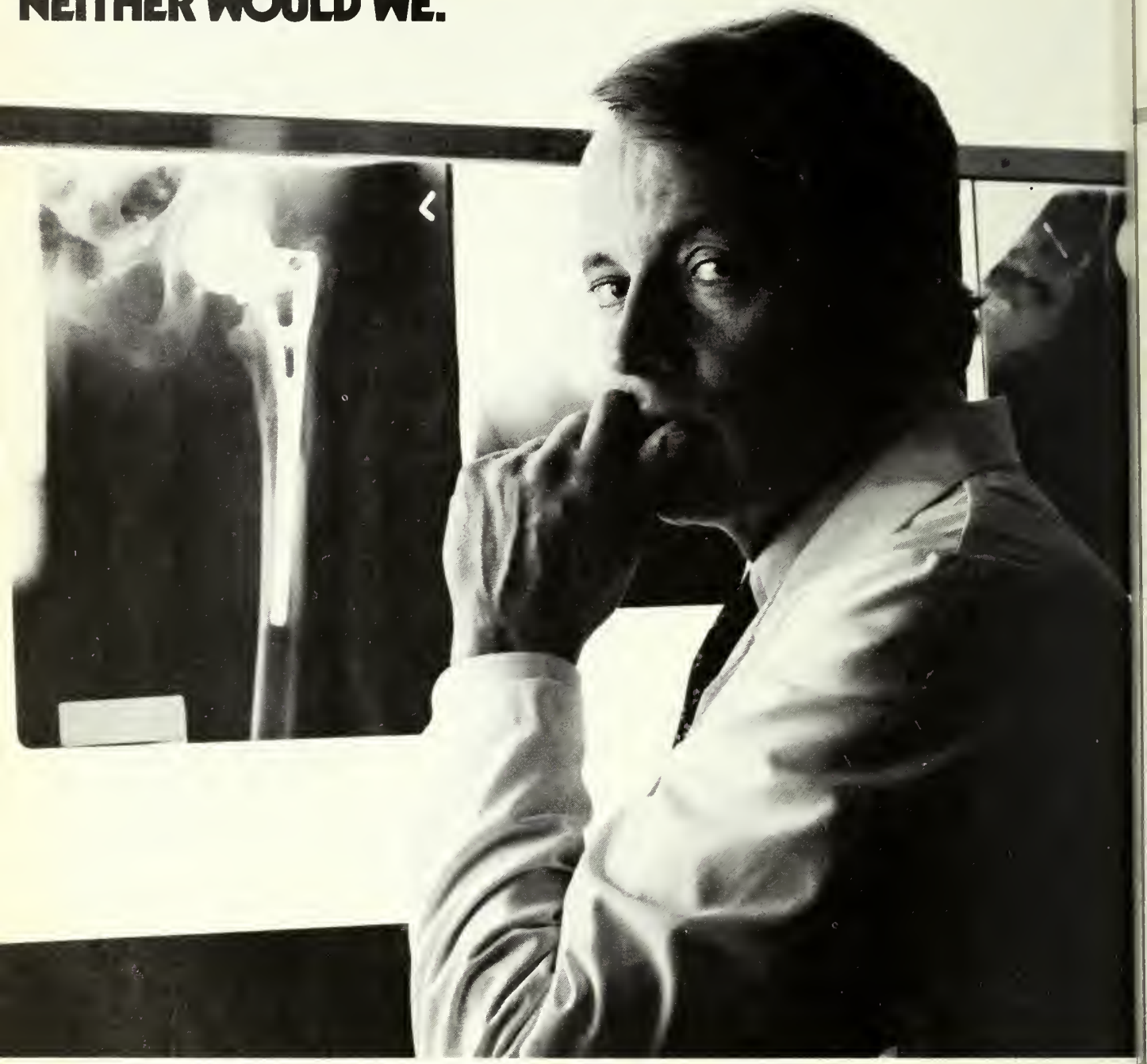
(213) 641-3297 TWX 910-328-6162 in CA 1 (800) 772-2666 ext. 904 in USA 1 (800) 227-2400 ext. 904

includes Alaska, Hawaii, Puerto Rico and the Virgin Islands

Brig Computers & Software is another division of the world wide services of Pax Consolidated Corporation.

WOULD YOU GUARANTEE THERE WON'T BE PROBLEMS OVER THE NEXT 5 YEARS?

NEITHER WOULD WE.



Responsible physicians know that despite sound medical judgment and specialized skills, their prognoses are often subject to uncertainty.

You must make allowances for potential adversity and you should expect your professional liability insurance company to do the same.

Responsible medical malpractice insurers, like The Doctors' Company, know that their policyholders' long-range interests are best protected by financial strength and solvency.

That's why we maintain the largest surplus of all the doctor-owned malpractice insurers in the western United States. That's why our earned premium to surplus ratio is the most favorable of all these companies. And that's why we continue to collect surplus contributions from new members.

Future results can't be guaranteed, in the fragile art of medicine or in the volatile business of malpractice insurance. Our allowance for adversity is surplus.

For details about our program, call or write: The Doctors' Company 233 Wilshire Blvd., Santa Monica, CA 90401. (213) 451-9936. Toll free, (800) 352-7271. Outside California, (800) 421-2368.

THE DOCTORS' COMPANY

AN INTERINSURANCE EXCHANGE
OFFERING MEDICAL MALPRACTICE INSURANCE
TO DOCTORS IN
CALIFORNIA, NEVADA, WYOMING AND MONTANA

THE WESTERN

Journal of Medicine

VOLUME 134 • NUMBER 2 **FEBRUARY 1981**

TABLE OF CONTENTS

97 *Amygdalin Toxicity Studies in Rats Predict Chronic Cyanide Poisoning in Humans*
GEORGE W. NEWTON, MA; ERIC S. SCHMIDT, BS; JERRY P. LEWIS, MD; ERIC CONN, PhD, and RUTH LAWRENCE, MD
From the Department of Internal Medicine, Section of Hematology and Onology, Section of Infectious and Immunologic Diseases, School of Medicine, and the Department of Biochemistry and Biophysics, College of Agriculture and Environmental Sciences, University of California, Davis.

104 *Breast Reconstruction for Premalignant and Malignant Disease—An Update*
DAVID B. APFELBERG, MD; BART MALDOWNEY, MD; DONALD R. LAUB, MD; MORTON R. MASER, MD, and HARVEY LASH, DDS, MD
From the Department of Plastic and Reconstructive Surgery, Comprehensive Center for Breast Disease, Palo Alto Medical Clinic, Palo Alto, California.

MEDICAL PROGRESS

109 *Disorders of Platelet Function—Mechanisms, Diagnosis and Management*
LOTHAR B. HUEBSCH, MD, and LAURENCE A. HARKER, MD
From the Department of Medicine, Hematology Division, University of Washington School of Medicine, Seattle.

SPECIALTY CONFERENCE

128 *The Use of Fibrinolytic Agents* Moderator: STANLEY I. SCHRIER, MD
Participants: ARTHUR A. SASAHARA, MD; ROBERT T. WALL, MD, and CHRISTINA B. HARBURY, MD
From the Division of Hematology, Department of Medicine, Stanford University School of Medicine, Stanford, California.
An edited transcript of a Conference held at Stanford University Medical Center. This transcript was edited by Robert T. Wall, MD.

MEDICAL STAFF CONFERENCE

134 *Seronegative Spondylarthritis* Chief Discussant: DAVID WOFSY, MD
A discussion selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from a transcription, it was prepared by Drs. David W. Martin, Jr, Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine.

IMPORTANT ADVANCES IN CLINICAL MEDICINE

Psychiatry—Epitomes of Progress
Items of progress in psychiatry. Each item in the judgment of a panel of knowledgeable physicians has recently become reasonably firmly established, both as to scientific fact and important clinical significance.

141 *Meditation: Clinical and Health-Related Applications* DEANE H. SHAPIRO, Jr, PhD

142 *The Diagnosis of Schizophrenia* MARVIN KARNO, MD

142 *Tardive Dyskinesia* THEODORE VAN PUTTEN, MD

143 *Screening for Endogenous Depression: The Dexamethasone Suppression Test*
VICTOR I. REUS, MD

143 *Pseudodementia Syndrome* EDWARD H. LISTON, MD

144 *The Therapeutic Alliance and the Outcome of Psychotherapy* CHARLES MARMAR, MD

144 *Cholinergic Hypersensitivity in Patients With Affective Disorders* DAVID S. JANOWSKY, MD

145 *Cognitive and Behavioral Psychotherapeutic Approaches to Depression*
RICARDO F. MUÑOZ, PhD

146 *Hyperkinetic Behavior Disorder* JAMES H. SATTERFIELD, MD

(Continued on Next Page)

EDITORIALS

147 *Hopes and No Hopes for the Next Quadrennium*

148 *Platelets in Perspective* JAMES G. WHITE, MD
From the Departments of Pediatrics, Laboratory Medicine and Pathology, University of Minnesota Medical School, Minneapolis.

149 *Has the Public's Interest in Health Care Peaked?*

149 *Why Thrombolytic Therapy* SOL SHERRY, MD
From the Department of Medicine, Temple University School of Medicine, Philadelphia.

CASE REPORTS

153 *Immunoglobulin D Myeloma—Report of a Case With Unusual Neurological Complications*
VINCENT CAGGIANO, MD; SURL L. NIELSEN, MD; FRANK J. GLASSY, MD, and DAVID F. DOZIER, Jr, MD
From the Department of Medicine, Hematology and Neurology Divisions, and the Department of Pathology, Neuropathology and Hematopathology Divisions, Mercy General Hospital and Sutter Community Hospitals, Sacramento, and the University of California, Davis, School of Medicine.

158 *Human Pulmonary Dirofilariasis in the West* FLAVIO CIFERRI, MD, MPH
From the Department of Medicine, Southern California Permanente Medical Group, Los Angeles.

162 *Severe Lactic Acidosis and Hypothermia* BRIAN J. MURRAY, MD
From the Department of Medicine, Mercy Hospital and Medical Center, San Diego.

CORRESPONDENCE

167 *Treatment of Heatstroke Victims* PETER G. HANSON, MD

167 *Tonsillectomy and Adenoidectomy* GORDON BREITMAN, MD

167 *Radiation Therapy for Skin Cancer* ERNST EPSTEIN, MD

168 *Possible Hazards of Nylon Athletic Shorts* ED SARGENT, MD

168 *TdT Negative T-ALL* STEPHEN LEE, MD, and DAVID ROSENBAUM, MD

169 *The Importance of Making Precise Medical Records in the 1980's* SAMUEL E. SPITAL, ESQ.

170 *Subacute Laetrile Intoxication*
RICHARD C. BARNETT, MD; JAMES POINTER, MD; JOHN NIMTZ, MD, and RICHARD BEERS, MD

172 *Private Enterprise Physicians, An Endangered Species?* JOHN M. DOUGLASS, MD

173 *High Altitude Flatus Expulsion (HAFE)* PAUL AUERBACH, MD, and YORK E. MILLER, MD

174 *Medicaid and the Medical Profession* EDWARD PALMER, MD

SPECIAL ARTICLE

175 *Physician Attitudes Toward Distressed Colleagues* JOHN N. CHAPPEL, MD
From the Department of Psychiatry and Behavioral Sciences, University of Nevada, Reno, School of Medicine.

HEALTH CARE DELIVERY

181 *Care of Mildly Ill Children Enrolled in Day-care Centers—Management by Parents and by Trained Home Workers*
ALBERT CHANG, MD, MPH; GEORGE KELSO, MD, MPH; MARCIA HARRIS, RN, and ALICE JORDAN, BA
From the Department of Social and Administrative Health Services, School of Public Health, University of California, Berkeley.

INFORMATION

186 *The Aging Heart—Observations in Patients 40 Years Old and Older*
RICHARD S. COSBY, MD; MARY MAYO, BA; ADRIAN MIREA, BS, and JAMES A. PETERSON, PhD
From the Foundation for Cardiovascular Research, Pasadena, California, and the Emeriti Center, University of of Southern California, University Park, Los Angeles.

BOOK REVIEWS

190 *Correlative Neuroanatomy & Functional Neurology—Seventeenth Edition*
by JOSEPH G. CHUSID, MD
Reviewed by EARL R. FERINGA, MD

190 *Fundamentals of Abdominal Sonography—A Teaching Approach*
by HOWARD W. RAYMOND, MD
Reviewed by KAI HABER, MD

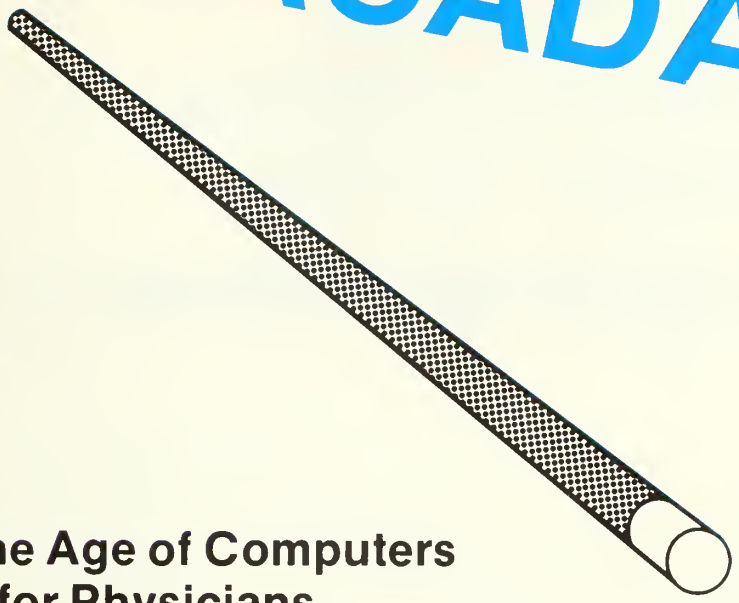
191 *In Memoriam*

Information for Authors, See January Issue, Advertising Page 10

CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA, HAWAII AND NEVADA, ALASKA, MONTANA AND IDAHO, OREGON, WASHINGTON, UTAH
(See Advertising Page 18)

Official Journal of the California Medical Association, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association and the Washington State Medical Association

ABRACADABRA



The Age of Computers for Physicians has APPEARED

It has been a long time MATERIALIZING AND there's no MAGIC about it . . . it's REAL!

WE'LL Show You At The CMA/WESTERN SCIENTIFIC ASSEMBLY on MARCH 14-16, 1981 . . . WE'RE HELIOSYSTEMS.

EXHIBIT #75 COME SEE THE FUTURE, NOW.

CLIP AND BRING THIS COUPON TO THE SHOW . . . IT'S MAGIC!

HELIO SYSTEMS

A division of Spectrum Management, Inc.

2195 Zanker Rd. ▪ San Jose, CA. 95131 ▪ (408) 946-6450

Without the innovators, there could be no imitators

Librium® C (chlordiazepoxide HCl) Roche
Premarin (conjugated estrogens) Ayerst Laboratories
HydroDiuril (hydrochlorothiazide) Merck Sharp & Dohme
Lanoxin (digoxin) Burroughs Wellcome Co.
Lasix (furosemide) Hoechst-Roussel
Meticorten (prednisone) Schering Corporation
Anturane (sulfinpyrazone) Ciba-Geigy Corporation
Erythrocin (erythromycin) Abbott Laboratories

Research and development, the life blood of pharmacotherapeutic progress

The drugs that have contributed so much to modern medicine were the product of long years of expensive research. And tomorrow's drugs depend upon continuation of the research and development going on right now. The cost of that research is one of the things reflected in the price of a brand-name drug. The substitution of a cheaper "generic" drug for a brand-name product may save the patient some money at the prescription counter. However, it threatens the very foundations of modern pharmaceutical research.

The hidden cost of "cheaper" generic drugs

Much of the enthusiasm for generic prescribing is based on a shortsighted view that fails to take such long-term issues into account. While cost is an important factor, pharmaceutical research, the quality of medicine, and future generations of patients must all be considered.

Settling for cheaper drugs today could deprive you and your patients of the drugs they may need tomorrow.

ROCHE®

To encourage imitation is to discourage innovation

CHECKING INTO MEDICAL MALPRACTICE INSURANCE?

CHECK OUT SOME FACTS	NORCAL MUTUAL Insurance Company	Physicians & Surgeons Insurance Exchange	The Doctor's Company
WHICH COMPANY IS DOCTOR OWNED ?	☑	☑	☑
WHICH DOES NOT REQUIRE SUBORDINATED LOAN/SURPLUS CONTRIBUTIONS ?	☑	☑	☐
WHICH IS RETURNING SUBORDINATED LOAN/SURPLUS CONTRIBUTIONS ?	☑	☐	☐
WHICH IS ENDORSED AND SPONSORED BY 24 LOCAL MEDICAL SOCIETIES ?	☑	☐	☐
WHICH HAS THE HIGHEST TOTAL ASSETS AND RESERVES ?	☑	☐	☐
WHICH HAS A SYSTEM OF PREMIUM CREDITS TOWARD RETIREMENT ? *	☑	☐	☐

NORCAL offers coverage to northern California physicians.

If you want more facts, call us toll-free at (800) 652-1051.

Or, call your Medical Society. They've been checking into medical malpractice insurance for years.

NORCAL MUTUAL INSURANCE COMPANY
333 Market Street, San Francisco, CA 94105
(415) 777-4200 or (800) 652-1051 (toll-free)

---

*NORCAL MUTUAL is the only company offering run-off premium credits to retiring physicians insured with the Company less than 5 years.

Come Visit Us at CMA Booth No. 97

SPOT-RESISTANT ORAL CONTRACEPTION IS HERE!

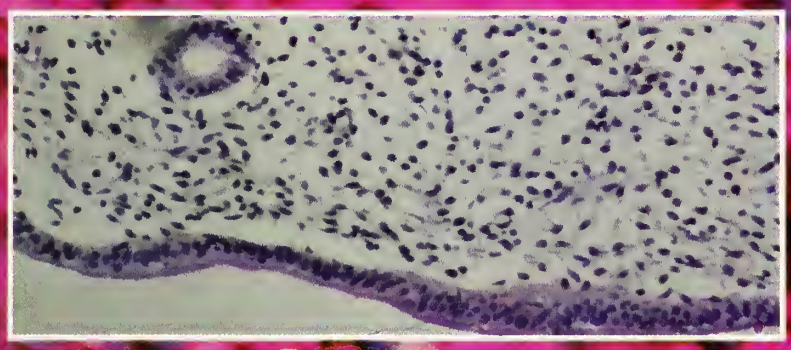
It's LO/OVRAL 30. And here's how it holds spotting and breakthrough bleeding to a minimum: Hormone balance right from the start...and throughout the cycle. Hormone balance made possible with a very low dose oral contraceptive because of the supportive progestational activity of norgestrel, Wyeth's exclusive progestogen.

Regular withdrawal bleeding, too despite its low dose. In clinical trials amenorrhea—defined as absence of bleeding in the 7 pill-free days—was reported in only 2.1% of total cycles. And when defined as absence of bleeding for 60 days or more (as it often is), the incidence was only 0.2%.*

And comfort for most patients* thanks to the same balance that helps prevent spotting and breakthrough bleeding. In the clinical trials, most patients stayed free of common side effects such as nausea (0.6% of cycles), vomiting (0.1%), depression (0.5%) and acne (0.9%).

Wyeth Laboratories
Philadelphia, Pa 19101

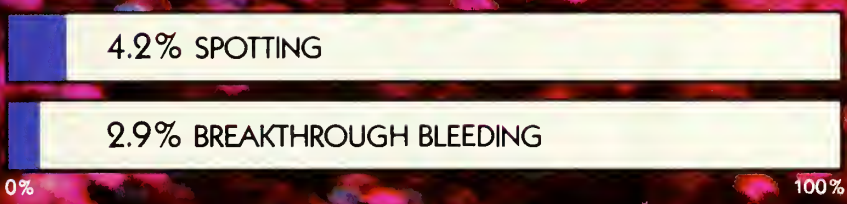
Copyright © 1980, Wyeth Laboratories. All rights reserved.



LO/OVRAL—1st cycle
Biopsy of intact endometrium in stable, progestogen suppressed state. Small, tubular gland in loose stroma without hemorrhage, fragmentation or debris characteristic of desquamating endometrium.

Even in the first cycle, the effective action of LO/OVRAL on the endometrium, such as you see here, provides the resistance against spotting and breakthrough bleeding you hope to achieve.

HISTOLOGICALLY... AND CLINICALLY.



A near-spotless record— in clinical trials involving 22,489 cycles*

*Serious as well as minor adverse reactions have been reported following the use of all oral contraceptives. Contraindications, Warnings, Precautions, Adverse Reactions, etc., in the accompanying In Brief should be carefully considered.

See full prescribing information.

LO/OVRAL® 30 mcg

each tablet contains 0.3 mg norgestrel with 0.03 mg ethinyl estradiol, Wyeth

...with a near-spotless record!

See important information on following page.

IN BRIEF:

Indications and Usage—LO/OVRAL® is indicated for the prevention of pregnancy in women who elect to use oral contraceptives (OC's) as a method of contraception

Contraindications—OC's should not be used in women with any of the following conditions: 1. Thrombophlebitis or thromboembolic disorders. 2. A past history of deep-vein thrombophlebitis or thromboembolic disorders 3. Cerebral-vascular or coronary-artery disease 4. Known or suspected carcinoma of the breast 5. Known or suspected estrogen-dependent neoplasia 6. Undiagnosed abnormal genital bleeding. 7. Known or suspected pregnancy (see Warning No. 5). 8. Benign or malignant liver tumor which developed during use of OC's or other estrogen-containing products.

Warnings

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious conditions, including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks

1. *Thromboembolic Disorders and Other Vascular Problems*—An increased risk of thromboembolic and thrombotic disease associated with use of OC's is well established. Three principal studies in Great Britain and 3 in the U.S. have demonstrated increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic. These studies estimate that users of OC's are 4 to 11 times more likely than nonusers to develop these diseases without evident cause.

CEREBROVASCULAR DISORDERS—In a collaborative American study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than nonusers and the risk of thrombotic stroke was 4 to 9.5 times greater in users than in nonusers.

MYOCARDIAL INFARCTION (MI)—An increased risk of MI associated with use of OC's has been reported, confirming a previously suspected association. These studies, conducted in the UK, found, as expected, that the greater the number of underlying risk factors for coronary artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of pre-eclamptic toxemia) the higher the risk of developing MI, regardless of whether the patient was an OC user or not. OC's, however, were found to be a clear additional risk factor. In terms of relative risk, it has been estimated that OC users who do not smoke (smoking is considered a major predisposing condition to MI) are about twice as likely to have a fatal MI as nonusers who do not smoke. OC users who are also smokers have about a 5-fold increased risk of fatal MI compared to users who do not smoke, but about a 10- to 12-fold increased risk compared to nonusers who do not smoke. Furthermore, amount of smoking is also an important factor. In determining importance of these relative risks, however, baseline rates for various age groups must be given serious consideration. Importance of other predisposing conditions mentioned above in determining relative and absolute risks has not as yet been quantified; quite likely the same synergistic action exists, but perhaps to a lesser extent.

RISK OF DOSE—In an analysis of data derived from several national adverse-reaction reporting systems, British investigators concluded that risk of thromboembolism, including coronary thrombosis, is directly related to dose of estrogen in OC's. Preparations containing 100 mcg or more of estrogen were associated with higher risk of thromboembolism than those containing 50-80 mcg. Their analysis did suggest, however, that quantity of estrogen may not be the sole factor involved. This finding has been confirmed in the U.S.

ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASES—A large prospective study carried out in the UK estimated the mortality rate per 100,000 women per year from diseases of the circulatory system for users and nonusers of OC's according to age, smoking habits, and duration of use. Overall excess death rate annually from circulatory diseases for OC users was estimated to be 20 per 100,000 (ages 15-34—5/100,000; ages 35-44—33/100,000; ages 45-49—140/100,000), risk being concentrated in older women, in those with long duration of use, and in cigarette smokers. It was not possible, however, to examine interrelationships of age, smoking, and duration of use, nor to compare effects of continuous vs. intermittent use. Although the study showed a 10-fold increase in death due to circulatory diseases in users for 5 or more years, all these deaths occurred in women 35 or older. Until larger numbers of women under 35 with continuous use for 5 or more years are available, it is not possible to assess magnitude of relative risk for this younger group. Available data from a variety of sources have been analyzed to estimate risk of death associated with various methods of contraception. Estimates of risk of death for each method include combined risk of contraceptive method (e.g., thromboembolic and thrombotic disease in the case of OC's) plus risk attributable to pregnancy or abortion in event of method failure. This latter risk varies with effectiveness of method. The study concluded that mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of DC's in women over 40 who smoke. Lowest mortality is associated with condom or diaphragm backed up by early abortion. Risk of thromboembolic and thrombotic disease associated with OC's increases with age after about 30 and, for MI, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of pre-eclamptic toxemia, and especially cigarette smoking. Physician and patient should be alert to earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

A 4- to 6-fold increased risk of postsurgery thromboembolic complications has been reported in OC users.

If feasible, OC's should be discontinued at least 4 weeks before surgery of a type associated with increased risk of thromboembolism or prolonged immobilization.

2. *Ocular Lesions*—There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis associated with use of OC's. Discontinue OC's if there is unexplained, sudden or gradual, partial or complete loss of vision, onset of proptosis or diplopia, papilledema, or retinal-vascular lesions, and institute appropriate diagnostic and therapeutic measures.

3. *Carcinoma*—Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases frequency of carcinoma of the breast, cervix, vagina, and liver. Certain synthetic progestogens, none currently contained in OC's, have been noted to increase incidence of mammary nodules, benign and malignant, in dogs. In humans, 3 case-control studies have reported an increased risk of endometrial carcinoma associated with prolonged use of exogenous estrogen in postmenopausal women. One publication reported on the first 21 cases submitted by physicians to a registry of cases of adenocarcinoma of the endometrium in women under 40 on OC's. Of cases found in women without predisposing risk factors (e.g., irregular bleeding at the time OC's were first given, polycystic ovaries), nearly all occurred in women who had used a sequential OC. These are no longer marketed. No evidence has been reported suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only OC's. Several studies have found no increase in breast cancer in women taking OC's or estrogens. One study, however, while also noting no overall increased risk of breast cancer in women on OC's, found an excess risk in subgroups of OC users with documented benign breast disease. Reduced occurrence of benign breast tumors in users of OC's has been well documented. In summary, there is at present no confirmed evidence from human studies of increased risk of cancer associated with OC's. Close clinical surveillance of all women on OC's is, nevertheless, essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer or with breast nodules, fibrocystic disease, or abnormal mammograms should be monitored with particular care if they elect to use OC's.

4. *Hepatic Tumors*—Benign hepatic adenomas have been found to be associated with use of OC's. One study showed that OC's with high hormonal potency were associated with higher risk than lower potency OC's. Although benign, hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage. This has been reported in short-term as well as long-term users. Two studies relate risk with duration of use of OC's, the risk being much greater after 4 or more years' use. While hepatic adenoma is rare, it should be considered in women presenting abdominal pain and tenderness, abdominal mass or shock. A few cases of hepatocellular carcinoma have been reported in women on OC's. Relationship of these drugs to this type of malignancy is not known.

5. *Use in or Immediately Preceding Pregnancy, Birth Defects in Offspring, and Malignancy in Female Offspring*—Use of female sex hormones—both estrogenic and progestational agents—during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, have increased risk of developing in later life a form of vaginal or cervical cancer ordinarily extremely rare. This risk has been estimated to be of the order of 1 in 1,000 exposures or less. Although there is no evidence now that OC's further enhance risk of developing this type of malignancy, such patients should be monitored with particular care if they elect to use OC's. Furthermore, 30 to 90% of such exposed women have been found to have epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether this condition is a precursor of vaginal malignancy. Male children so exposed may develop abnormalities of the urogenital tract. Although similar data are not available with use of other estrogens, it cannot be presumed they would not induce similar changes. An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with use of sex hormones, including OC's, in pregnancy. One case-control study estimated a 4.7-fold increase in risk of limb-reduction defects in infants exposed in utero to sex hormones (OC's, hormonal withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some exposures involved only a few days. Data suggest that risk of limb-reduction defects in exposed fetuses is somewhat less than 1 in 1,000 live births. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective. There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing OC's. Embryos with these anomalies are virtually always aborted spontaneously. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping OC's is unknown. It is recommended that, for any patient who has missed 2 consecutive periods, pregnancy should be ruled out before continuing OC's. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at time of first missed period, and further use of OC's should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus, and advisability of continuation of the pregnancy should be discussed. It is also recommended that women who discontinue OC's with intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive. Many clinicians recommend 3 months, although no precise information is available on which to base this. The administration of progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy.

6. *Gallbladder Disease*—Studies report increased risk of surgically confirmed gallbladder disease in users of OC's and estrogens. In one study, increased risk appeared after 2 years' use and doubled after 4 or 5 years' use. In one of the other studies, increased risk was apparent between 6 and 12 months' use.

7. *Carbohydrate and Lipid Metabolic Effects*—Decrease in glucose tolerance has been observed in a significant percentage of patients on OC's. For this reason, prediabetic and diabetic patients should be carefully observed while on OC's. Increase in triglycerides and total phospholipids has been observed in patients on OC's, clinical significance of this finding remains to be defined.

8. *Elevated Blood Pressure*—Increase in blood pressure has been reported in patients on OC's. In some women, hypertension may occur within a few months of beginning OC's. In the 1st year of use, prevalence of women with hypertension is low in users and may be no higher than that of a comparable group of nonusers. Prevalence in users increases, however, with longer exposure, and in the 5th year of use is 2½ to 3 times the reported prevalence in the 1st year. Age is also strongly correlated with development of hypertension in OC users. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure on OC's. Hypertension that develops as a result of taking OC's usually returns to normal after discontinuing the drug.

9. *Headache*—Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of OC's and evaluation of the cause.

10. *Bleeding Irregularities*—Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing OC's. In breakthrough bleeding, as in all cases of irregular vaginal bleeding, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or change to another OC may solve the problem. Changing to an OC with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary, since this may increase risk of thromboembolic disease. Women with past history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrheic after discontinuing OC's. Women with these pre-existing problems should be advised of this possibility and encouraged to use other methods. Post-use anovulation, possibly prolonged, may also occur in women without previous irregularities.

11. *Ectopic Pregnancy*—Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

12. *Breast-feeding*—OC's given in the postpartum period may interfere with lactation and decrease quantity and quality of breast milk. Furthermore, a small fraction of the hormones in OC's has been identified in the milk of mothers on OC's, effects, if any, on the breast-fed child have not been determined. If feasible, defer OC's until infant has been weaned.

Precautions—GENERAL—1. A complete medical and family history should be taken prior to initiation of OC's. Pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Pap smear and relevant laboratory tests. As a general rule OC's should not be prescribed for longer than 1 year without another physical examination.

2. Under influence of estrogen-progestogen preparations, pre-existing uterine leiomyomata may increase in size.

3. Patients with history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while on OC's should stop OC's and use an alternate method to try to determine whether the symptom is drug-related.

4. OC's may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, asthma, or cardiac or renal insufficiency.

5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence while on OC's. If jaundice develops, OC's should be discontinued.

6. Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution.

7. OC users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency. Clinical significance is undetermined.

8. Serum folate levels may be depressed by OC's. Since the pregnant woman is predisposed to development of folate deficiency and incidence of folate deficiency increases with increasing gestation, it is possible that if a woman becomes pregnant shortly after stopping OC's, she may have a greater chance of developing folate deficiency and complications attributed to this deficiency.

9. The pathologist should be advised of OC therapy when relevant specimens are submitted.

10. Certain endocrine- and liver-function tests and blood components may be affected by estrogen-containing OC's: a. Increased sulfobromophthalein retention. b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. c. Increased thyroid-binding globulin (TBG) leading to increased circulating total-thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered. d. Decreased pregnanediol excretion. e. Reduced response to metyrapone test.

Information for the Patient—See Patient Package Labeling.

Drug Interactions—Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin. A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, ampicillin and tetracycline.

Carcinogenesis—See Warnings on carcinogenic potential of OC's.

Pregnancy—Category X. See Contraindications, Warnings.

Nursing Mothers—See Warnings.

Adverse Reactions—An increased risk of these serious adverse reactions has been associated with use of OC's (see Warnings): thrombophlebitis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, cerebral hemorrhage, hypertension, gallbladder disease, benign hepatomas, congenital anomalies. There is evidence of an association between the following conditions and use of OC's although additional confirmatory studies are needed: mesenteric thrombosis, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions have been reported in patients on OC's and are believed to be drug-related: Nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10 percent or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally: Gastrointestinal symptoms (such as abdominal cramps and bloating); breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhea, amenorrhea during and after treatment, temporary infertility after discontinuance of treatment, edema; chloasma or melasma which may persist, breast changes: tenderness, enlargement, and secretion; change in weight (increase or decrease), change in cervical erosion and cervical secretion; possible diminution in lactation when given immediately postpartum, cholestatic jaundice, migraine, increase in size of uterine leiomyomata, rash (allergic), mental depression, reduced tolerance to carbohydrates, vaginal candidiasis, change in corneal curvature (steepening), intolerance to contact lenses.

The following adverse reactions have been reported in users of OC's, and the association has been neither confirmed nor refuted: premenstrual-like syndrome, cataracts, changes in libido, chorea, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, vaginitis, porphyria.

Acute Overdose—Serious ill effects have not been reported following acute ingestion of large doses of OC's by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

LO/OVRAL® each tablet contains 0.3 mg norgestrel with 0.03 mg ethinyl estradiol

Wyeth Laboratories Phila., Pa. 19101

Classified Advertisements

The rate for each insertion is **4.00 per ine** (average six words per line) **with ive line minimum.**

Box number charge: $2.00 each month.

Classified display rates $40.00 per inch.

Copy for classified advertisements should be eceived not later than **the fifth of the month** receding issue. **All copy must be typed or rinted.** • Classified advertisers using Box Numers forbid the disclosure of their identity. Your nquiries in writing will be forwarded to Box lumber advertisers. The right is reserved to eject or modify all classified advertising copy n conformity with the rules of the Advertising Committee.

Please Type or Print Advertising Copy

CLASSIFIED ADVERTISEMENTS ARE PAYABLE IN ADVANCE

PHYSICIANS WANTED

AMILY PRACTITIONER, Bd. Elig./Cert., for evelopment of family practice succeeding eighborhood clinic in San Francisco. Salary 40,000-$45,000. Please write or call collect: eorge Hunt, Director of Ambulatory Services, acific Medical Center, P.O. Box 7999, San rancisco, CA 94120. (415) 921-5156. EOE-MFH.

CALIFORNIA, San Jose: Primary Care Physician ith experience in Peds. and minor trauma anted to staff ambulatory care clinic at large aching hospital in San Francisco Bay Area. lexible hours, independent contractor status ith hourly compensation. For further details, lease call or write: Eve Campbell, 1550 The lameda, No. 314, San Jose, CA 95126. Tele: 408) 293-8881.

AN FRANCISCO BAY AREA—45-MD multispecilty private group practice established 25 years go, seeking an orthopedic surgeon for medical/dustrial office work to assist our busy 2 physician department in their general orthopedic ork. Excellent location in the Santa Clara Vaey, 45 minutes from San Francisco, 10 minutes om Stanford University. Send CV to: Walter aphir, MD, Sunnyvale Medical Clinic, 596 Carll St., Sunnyvale, CA 94086.

DEVELOPMENTAL DISABILITIES PROGRAMS

Opportunities are available for internists, family practitioners and psychiatrists to work with developmentally disabled people in State residential communities. Locations from Los Angeles to northern California. Challenging and varied cases, congenial professional environment, excellent civil service benefits.

Hospital Recruitment Program
Dept. of Developmental Services
714 P Street
Sacramento, CA 95814
(916) 322-1221 collect

PHYSICIANS WANTED

OBSTETRICIAN/GYNECOLOGIST WANTED to join the OB/GYN Department of Magan Medical Clinic, Inc., a 31 physician multispecialty group practice located in Southern California near Los Angeles. Call or send CV to Dale H. Weifenbach, MD, Magan Medical Clinic, Inc., 420 W. Rowland St., Covina, CA 91723. (213) 331-6411.

GROW WITH US IN SUNNY ARIZONA—The INA Healthplan needs physicians in family practice and most specialties in Tucson and Phoenix. Attractive salaries and comprehensive benefits including a professional development program, retirement plan, and group incentive bonus are provided. If team interaction and casual living appeal to you, send your CV to: Professional Relations, INA Healthplan, Inc., 6115 North 7th Street, Phoenix, AZ 85014.

GENERAL SURGEON—needed in established multispecialty clinic in beautiful university town. First year guaranteed with full fringe benefits and incentive, new hospital, four season recreation, and ideal family environment. Contact The Budge Clinic, 225 E. 4th North, Logan, UT 84321.

WANTED: Univ. trained general surgeon needed to join two other general surgeons in 13 man clinic. Excellent qualifications required. Location: southern Idaho, near excellent outdoor recreation. Write Box 1233, Twin Falls, ID 83301.

OTOLARYNGOLOIST—Solo practice in beautiful Pacific Northwest coastal city. Excellent school system, University in city, abundant recreational opportunities. Must be board certified or eligible, aggressive and hard working. Reply Box 6156, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

ORTHOPEDIC SURGEON—Board Certified, Orthopedic Surgeon needed at VA Medical Center, Livermore, CA. Ideal living, good climate and clean air. Malpractice insurance not needed. Position available at present. Salary dependent upon experience and qualifications. Contact: John F. Kane, MD, Chief of Staff, VA Medical Center, Livermore, CA 94550. Tel: (415) 447-2560, ext. 204.

EMERGENCY MEDICINE OPPORTUNITIES, full and part-time, in the Rocky Mountain states for career oriented emergency physicians. Excellent compensation and paid professional liability insurance. Send credentials to Mr. William Salmo, Chase Stone Center, Holly Sugar Building, Suite 440, Colorado Springs, CO 80903. Or call toll-free 1 (800) 525-3681 (in Colorado call collect (303) 471-4981).

COALINGA, CALIFORNIA: Rare opportunity in town of 10,000 for solo GP/FP. No night or weekend call. Guarantee, paid malpractice, profit sharing, 90 percent private patients. Contact: Carol Sweig, Western Physicians, 1124 Ballena Bl., Alameda, CA 94501. (415) 521-4110.

GENERAL PRACTITIONERS SPECIALISTS—Are you considering a practice change, please call us, let's talk. We have many opportunities in various West Coast locations. If you would like to join a group, associate or own your own practice we can help. Call us collect at (714) 997-0853, or send CV to Physicians Search Associates, 1201 W. La Veta, Suite No. 209, Orange, CA 92668.

YUBA CITY-MARYSVILLE—Outstanding opportunity for medical practice. Office in established professional building for lease. Growing area. Reasonable terms. Call collect Gayla Stallins (916) 674-1330.

DIRECTOR, UNIVERSITY OF UTAH RESIDENCY PROGRAM. Full-time faculty positions, physicians with knowledge and experience in Family Practice. Responsible for intergration and expansion of an established residency program at the University of Utah, EOE. Medical Center, Salt Lake City, UT 84132. C. Hilmon Castle, MD, 50 North Medical Drive, Salt Lake City, UT 84132.

UCLA FACULTY DEVELOPMENT FELLOWSHIP

Do you still maintain an intellectual interest in the practice of Medicine? Did your training stop short of your Ideal? Are you entertaining an interest in teaching? Would you be willing and able to deliver patient care in the area served by Family Practice at UCLA; i.e. Pediatrics, Nursery, Obstetrics, Medicine, and ICU? If willing to spend twelve months seeking answers to these questions, please write: Wm. MacMillan Rodney, MD, UCLA Family Practice, BH-134 CHS, Los Angeles, CA 90024. UCLA is an equal opportunity affirmative action employer.

FINANCIAL REWARDS and PROFESSIONAL SATISFACTION . . . . . plus a whole lot more, Doctor!

We offer physician salaries in all specialties including General Practitioner and Family Practitioner that are among the highest paid in the nation and our benefit package (including malpractice insurance) is unexcelled.

Our quality of care is excellent; our medical facilities are attractive and efficient; and our climate for both living and working is outstanding.

We are one of the largest Federally-approved HMO's in the U.S., and we currently have a few very desirable positions available in the Los Angeles area. If you are interested, please call or write:

INA HEALTH PLAN OF CALIFORNIA
1880 Century Park East
Los Angeles, CA 90067
Phone (213) 553-6677, Extension 364
Attn.: Mr. Yoakam
Director of Physician Services

Excellent opportunities exist in prime geographical locations throughout the Western, Midwestern and Rocky Mountain states for General and Family Practice Physicians. Access to hunting, fishing, skiing, boating and other excellent recreational activities. Top school systems and warm community atmosphere. Unlimited opportunity to make an Impact. Compensation package Includes base guarantee, incentives and fringe benefits. Complete medical practice support. The future holds unlimited growth potential. For information contact:

AHS
Advanced Health Systems, Inc.
Professional Placement
17861 Cartwright Road
Irvine, CA 92714
or call toll-free (800) 854-3020
EOE M/F

PHYSICIANS WANTED

FRESNO-BAKERSFIELD-OXNARD. Family Medical Center, a primary care group practice, has positions available for Bd. Cert./Elig. Gen. Pract. or Internist. Minimum guarantee, partnerships available. New facilities, all administrative services provided. Contact: S. Lee, P.O. Box 8013, Fresno, CA 93747. (209) 252-1618.

(Continued on Page 16)

(Continued from Page 15)

PHYSICIANS WANTED

INFECTIOUS DISEASE Specialist wanted to join another busy ID Specialist in private practice in growing city in Northwest. Please send CV to Box 6163, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

CARDIOLOGIST, Board certified or eligible trained in heart catheterization for four man cardiology group, affiliated with large Cardiovascular Center. Referral practice located near Los Angeles. University affiliation available. Immediate partnership, nothing to buy. Equal work, pay and time off. Call (213) 866-3716.

OPHTHALMOLOGIST to join established ophthalmologist in Los Angeles area. Must be well-trained and motivated. Preferably interested in permanent association (partnership). Send CV to Box 6154, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

CALIFORNIA—B.E./B.C. Family Physician, Emergency Physician or Internist wanted for new multi-Specialty group in desirable Roseville suburb of Sacramento. Combines office practice with part-time Minor Emergency Clinic practice. Competitive salary. Fringe; leads to partnership. Excellent hospital and office facilities. One position avail. immed., one avail. in Spring, 1981. Contact: Joseph Rosenfield, Adm., Western Medical Group, 6330 Main Ave., Orangevale, CA 95662, (916) 988-9544.

CARDIOLOGIST—Excellent opportunity to associate with young 2 man consultative practice in coastal California. Must be skilled in pacemakers, Swan Ganz technique. Please send résumé, references. Box 6170, Western Journal of Medicine, 731 Market St., San Francisco CA 94103.

LARGE SOUTHERN CALIFORNIA Internal Medicine and Medical Subspecialty group is seeking an internist with subspecialty in rheumatology. Contact P.O. Box 22683, San Diego, CA 92122.

PHYSICIANS WANTED

RADIOLOGIST: Board certified, experienced all major modalities plus board eligible and/or certified in nuclear medicine or equivalent, join group in hospital practice Southern California. Full curriculum vitae initial reply, Box 6177, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

EMERGENCY DEPARTMENT OPENING—Permanent and Part-Time in our group. First year salary of $78,000 includes profit sharing and pension plan, educational allowance health insurance, and part time paid at $50 per hour. Malpractice paid. Full time averages less than 40 hours per week. ED sees 43,000 annually in a 300 bed acute care hospital located in Fresno, CA. Near the High Sierras and other recreational areas. Contact Larry Marks, MD, 546 W. Morris, Fresno, CA 93704, or call collect (209) 431-3645.

CALIFORNIA: Faculty member for Family Practice Residency Program located in Orange County. Prefer Residency trained, Board Certified Family Physician. Practice and/or teaching experience preferred. Responsibilities include In-patient coordination of Residency Program or Out-Patient teaching activities. Salary negotiable. Program affiliated with University of Southern California, School of Medicine. Send all inquiries and CV to: J. Blair Pace, MD, Director, Family Practice Residency Program, Santa Ana-Tustin Community Hospital, 1001 North Tustin Avenue, Santa Ana, CA 92705. Phone: (714) 835-3555.

FELLOWSHIP IN DIABETES-ENDOCRINOLOGY available. Excellent opportunity for clinical and research experience. The two year fellowship (starting 7/81) leads to Board qualification in Endocrinology and Metabolic Diseases. For further information send C.V. to: Loren G. Lipson, MD, Diabetes Section, University of Southern California School of Medicine, 2025 Zonal Ave., Los Angeles, CA 90033. USC is an Affirmative Action/Equal Opportunity Employer.

PHYSICIANS WANTED

INTERNIST/GI to join a 13-physician, multi-specialty group in Mount Vernon, Washington. The Medical Center is located across the street from a 126-bed hospital. Stockholder status is possible after one year. Guaranteed first year salary plus liberal fringe benefits. Position available June, 1981. Contact Shane Spray, Administrator, Skagit Valley Medical Center, 1400 Kincaid, Mount Vernon, WA 98273. (206) 428-2524.

SAN FRANCISCO. GP, FP, or Internist to join 3 man FG group, must be interested to become partner after 1 year. Adjacent St. Luke's Hospital. For further details call or write, L. D. Duffield, MD, 3620 Army St., San Francisco, CA 94110. Tel: (415) 826-7575.

MEDICAL OPHTHALMOLOGIST wanted in Southern California near retirement community. Box 6172, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

ER MEDICAL DIRECTOR—200+ Bed Southern Cal. Hosp. seeks BRD. Cert/Elig. MD with emergency specialty. Lucrative from start; great future. Very desirable location. Beyond technical proficiency, individual must have strong business and management capabilities. Send c.v. immed. to Box 6171, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

SANTA BARBARA, CALIFORNIA—53 Physician Group Practice has immediate openings in: Family Practice, Nephrology, Obstetrics/Gynecology, Oncology, Orthopedic Surgery, Pulmonary Disease, Urology, to join expanding departments in multi-specialty clinic in operation since 1921. Excellent benefit package. Must have U.S. citizenship, Board certified or eligible. CV to: Administration, Santa Barbara Medical Foundation Clinic, P.O. Box 1200, Santa Barbara, CA 93102.

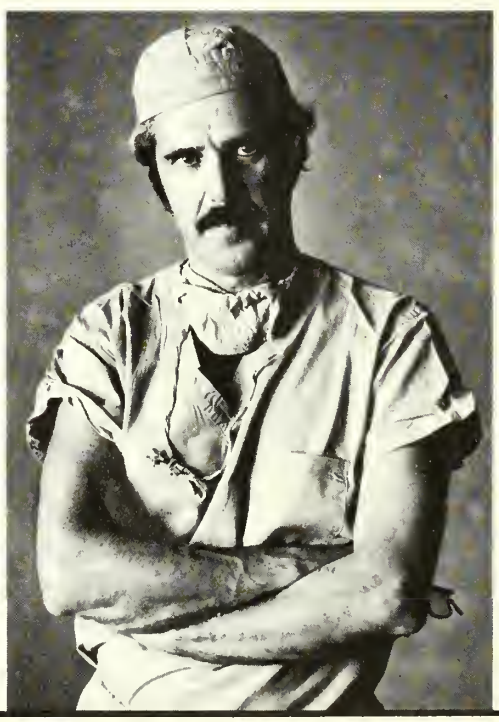
(Continued on Page 37)

We've taken the pain out of establishing your practice.

As a physician you're familiar with ways to alleviate pain. But chances are, your extensive educational process has not prepared you to handle the problems of selecting a location and establishing a successful private practice. National Medical Enterprises' Professional Relations Department has a staff of highly trained people who can help take the anguish out of making this important decision.

If you are familiar with NME you know us as one of America's largest and fastest growing health care companies that owns, operates, and manages acute care facilities that meet or exceed JCAH standards.

NME can provide Board Eligible/Board Certified physicians with private practice opportunities from Seattle, Washington to St. Petersburg, Florida - opportunities that enable you to concentrate on medicine while we assist you through the start-up phase of your new practice.



NME can offer you some of the best equipped health care facilities in the nation along with modern offices, a diverse choice of climates and a community ideally suited to your lifestyle.

Let us take the pain out of establishing a practice for you. Write and send us your curriculum vitae. Let us know your interests and where you want to live and practice. For additional information, contact:

Raymond C. Pruitt
Director, Physician Relations
National Medical Enterprises
11620 Wilshire Blvd.
Los Angeles, California 90025
(213) 479-5526
1-800-421-7470

NME NATIONAL MEDICAL ENTERPRISES, INC.

"The total health care company."

Leadership

It took time to achieve it
It takes dedication to keep it

Purepac became the largest generic drug manufacturing facility in the United States by providing high quality generic pharmaceuticals at the lowest possible cost. We know that to be on top tomorrow, we've got to stay a few steps ahead today. Here are some of the steps we've already taken:

- **Full-time Medical Vice President with Supporting PhD Staff**
- **ANDA/Patent Review Departments**
- **State Formulary Manager**
- **Regulatory Affairs Department**
- **Comprehensive Advertising and Marketing Support Programs**

It took Purepac 50 years to achieve this leadership position. And we're determined to provide you with even more quality products and dedicated services in the next 50 years.

PUREPAC PHARMACEUTICAL CO.
Division of Kalipharma, Inc., Elizabeth, N.J. 07207

1930-1981

Celebrating over 50 years of industry leadership.

GN-1080

CONTINUING MEDICAL EDUCATION

California, Hawaii, Nevada • Alaska, Montana, Idaho • Oregon • Washington • Utah

CALIFORNIA, HAWAII and NEVADA

This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000, ext. 146. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

March 14-21—**9th Obstetric Anesthesia Conference.** Ohio State Univ. at Sheraton Waikiki, Honolulu. One week. 25 hrs. Contact: Excursions Unlimited, Inc., c/o OSU Dept. of Anesthesiology, 1820 Northwest Blvd., Columbus, OH 43212. (800) 848-4438.

April 6-10—**California Society of Anesthesiologists—Hawaiian Seminar.** Kauai Surf Hotel, Kauai. Monday-Friday. 26 hrs. $200, members; $250, nonmembers. Contact: CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

May 3-9—**17th Biennial Western Conference on Anesthesiology.** Hawaiian Regent Hotel, Waikiki (3-7) and Intercontinental Hotel, Maui (8-9). One week. 26 hrs. Contact: Biennial Western Conf. on Anesthesiology, Group Travel Unlimited, 700 Larkspur Landing Circle, Suite 169, Larkspur 94939.

June 4-7—**California Society of Anesthesiologists—Annual Scientific Meeting.** Hyatt Regency, San Francisco. Thursday-Sunday. 20 hrs. $100, members; $200, nonmembers. Contact: CSA, 100 E. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

August 23-25—**Neuro-Anesthesia.** UCSD at Village Inn, La Jolla. Sunday-Tuesday.

CANCER

February 21—**Investigational Methods of Cancer Treatment.** San Francisco Unit, American Cancer Society, and San Francisco Regional Cancer Foundation at Fireman's Fund Building, San Francisco. Saturday. 4 hrs. $15. Contact: Terry Sheehy, PhD, S.F. Regional Cancer Fndn., 14th Ave. and Lake St., San Francisco 94118. (415) 221-2132.

February 23-26—**Advances in Clinical Practice of Hematology/Oncology.** See Medicine, February 23-26.

February 25—**Ovarian Cancer.** Hospital of the Good Samaritan at Hilton, Los Angeles. Wednesday. 7 hrs. Contact: Mary Jane Thompson, Hosp. of the Good Samaritan, 616 S. Witmer St., Los Angeles 90017. (213) 488-8908.

February 28-March 1—**Recent Advances in Cancer Diagnosis.** UCLA. Saturday-Sunday.

March 6-8—**Current Approaches to Radiation Oncology, Biology and Physics.** See Radiology, March 6-8.

March 8-13—**19th National Conference on Breast Cancer.** American College of Radiology, American Cancer Society, College of American Pathologists at Hotel del Coronado, Coronado. Sunday-Friday. 33 hrs. $275. Contact: ACR, 6900 Wisconsin Ave., Chevy Chase, MD 20015. (301) 654-6900.

March 13-14—**Childhood Cancer: Triumph Over Tragedy—16th Annual Cancer Symposium.** West Coast Cancer Foundation and Calif. Division of American Cancer Society at Hyatt Regency, San Francisco. Friday-Saturday. 12 hrs. $110 before February 1; $130 thereafter. Contact: WCCF, 50 Francisco St., Suite 200, San Francisco 94133. (415) 981-4590.

April 25—**Oncology Update: 1981.** Northridge Hospital at Century Plaza Hotel, Los Angeles. Saturday. 8 hrs. $125. Contact: Sandra Rozzen, Dept. of Med. Ed., Northridge Hosp., 18300 Roscoe Blvd., Northridge 91328. (213) 885-5311.

May 18-22—**Medical Oncology Review.** American College of Physicians at University of Hawaii School of Medicine, Honolulu. Monday-Friday. Contact: Postgraduate Dept., ACP, 4200 Pine St., Philadelphia, PA 19104. (215) 243-1200.

June 10—**Carcinomas of the Uterus and Ovaries.** LLU. Wednesday. 4 hrs. $30.

June 13-17—**Head and Neck Oncology.** UCLA. Saturday-Wednesday.

EMERGENCY MEDICINE

February 16-19—**Emergency Medicine: New Concepts in Resuscitation.** UCD at Hyatt Lake Tahoe, Incline Village. Monday-Thursday. 19¼ hrs.

(Continued on Page 23)

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center 2801 Atlantic Ave., Long Beach 90801. (213) 595-3837.

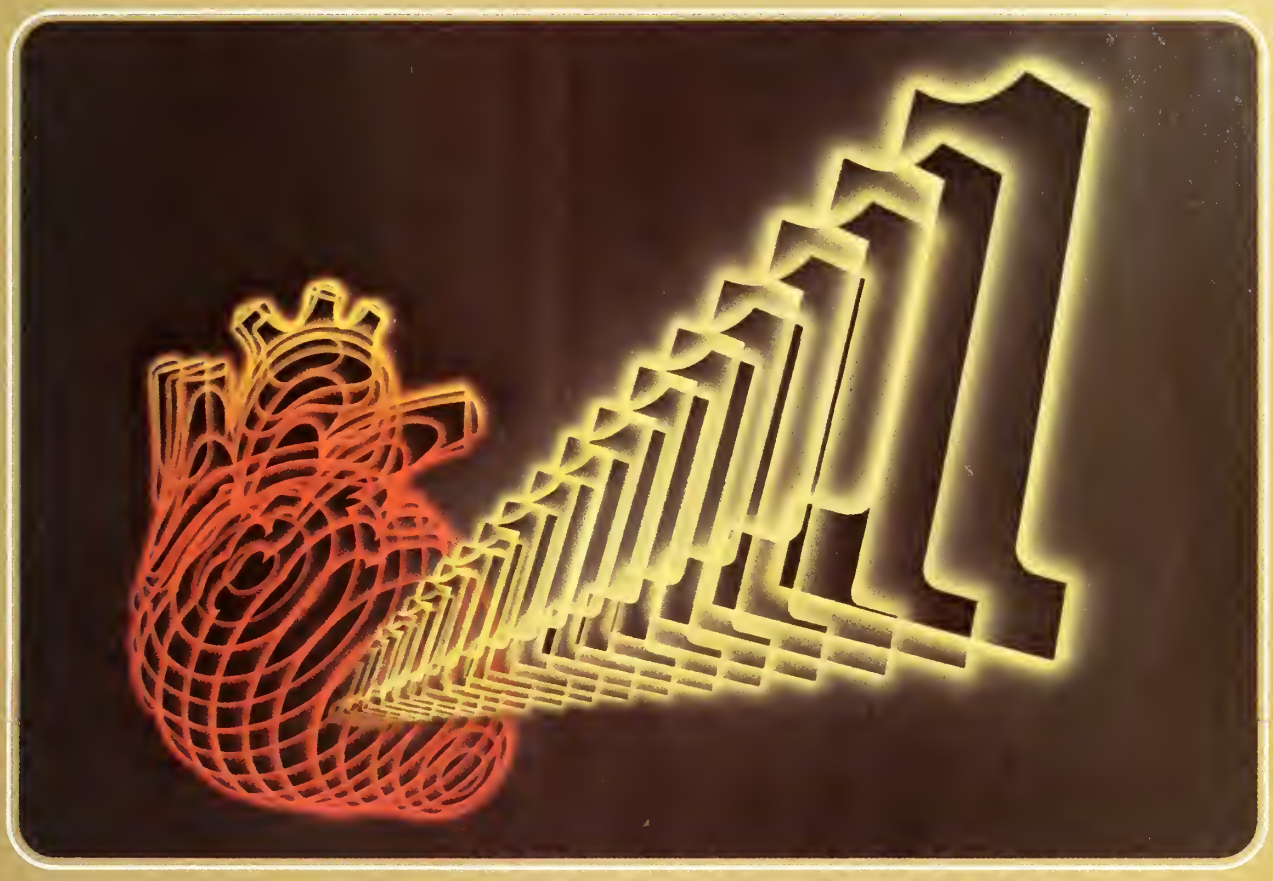
UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Lolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

CORGARD®
nadolol tablets

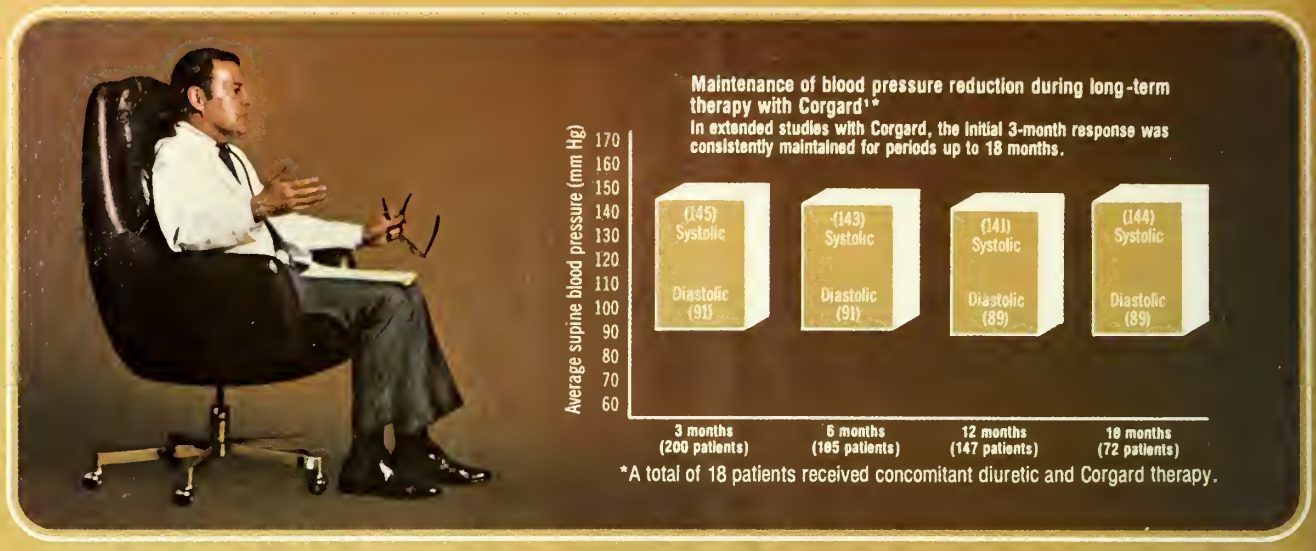


The first beta-blocker with once-a-day dosage

Round-the-clock protection in the control of hypertension

SQUIBB®

See last page of this advertisement for brief summary.



When you prescribe...

CORGARD® [nadolol tablets] ...for significant blood pressure reduction

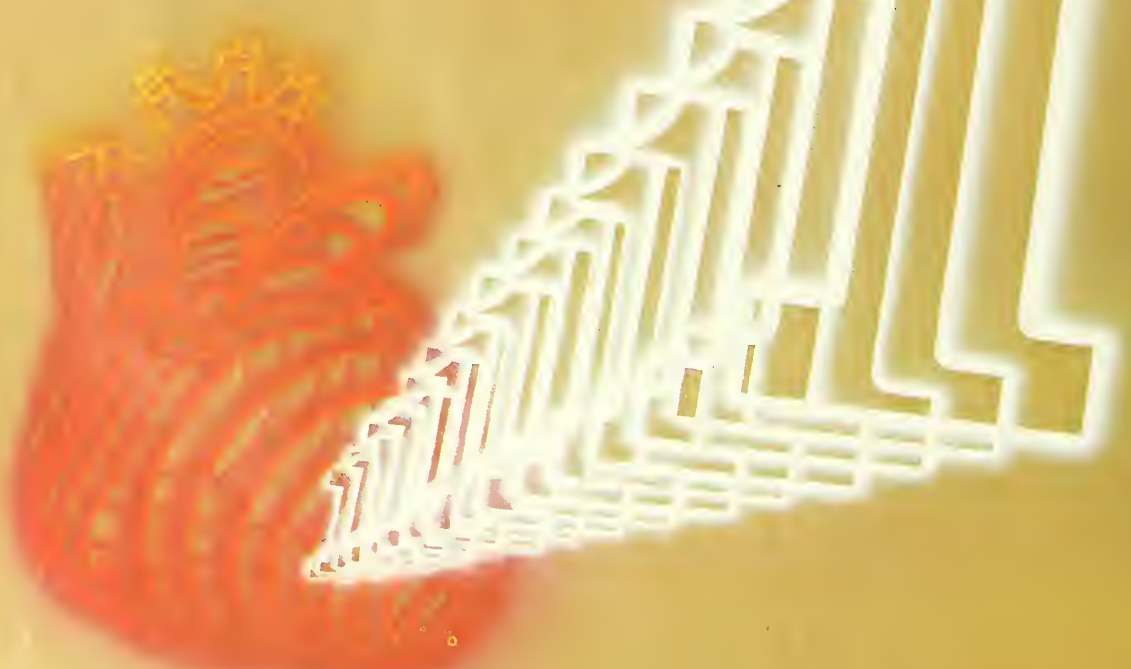
In short-term clinical studies of 114 patients with mild, moderate and severe hypertension, Corgard taken in single daily doses of 40–320 mg (mean: 200 mg) achieved a significant overall reduction in supine and standing blood pressure in 94% of patients — this included 62.3% of the patients who achieved normalized supine diastolic pressure (≤ 90 mm Hg).

...for comparable efficacy, once a day, to propranolol, four times a day

In a controlled clinical comparison of 179 patients with mild, moderate and severe hypertension, Corgard, once a day, was as effective in reducing supine and standing pressure as propranolol, four times a day.[1]

...for extended protection in control of mild, moderate and severe hypertension

Corgard provides round-the-clock control of hypertension by reducing elevated systolic and diastolic blood pressure — with a single daily dose.



They can comply.

CORGARD® [nadolol tablets] ...promotes compliance with a single daily dose

The 20- to 24-hour serum half-life of Corgard offers round-the-clock reduction in blood pressure with a once-daily dosage. With no need to interrupt daily activities to take multiple doses of medication, patients are more likely to comply.

...is often effective alone, without a diuretic[1]

Control of blood pressure with a single agent also simplifies the patient's medication schedule. Only one medication once a day means less likelihood of forgotten or skipped doses.

...rarely causes impotence, loss of libido, orthostatic hypotension*

Because it is virtually free from these undesirable side effects, the patient can function normally, without undue concern.

Prescribe

CORGARD®
nadolol tablets

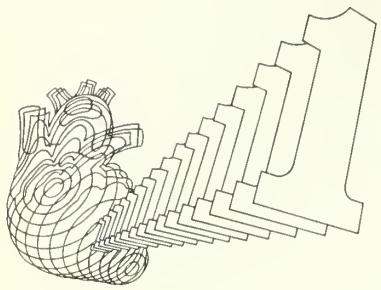
40 mg, 80 mg, 120 mg, and 160 mg tablets

The common-sense beta-blocker for hypertension

SQUIBB®

*Please see brief summary for discussion of Contraindications, Adverse Reactions, Precautions, and Warnings, including avoidance of abrupt withdrawal, on next page of this advertisement.

The only once-a-day beta-blocker for both hypertension and angina pectoris



CORGARD®
nadolol tablets
40 mg, 80 mg, 120 mg, 160 mg scored tablets

CORGARD® TABLETS
Nadolol Tablets

DESCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery — Because beta-blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** — Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory** — Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** — Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System** — reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal** — mesenteric arterial thrombosis; ischemic colitis. **Hematologic** — agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic** — fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous** — reversible alopecia; Peyronie's disease; erythematous rash.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm — Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to 160 mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval — see package insert for dosage in these patients.

For full prescribing information, consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and 1000 tablets and in Unimatic® single-dose packs of 100 tablets.

Reference:
1. Data on file, Squibb Institute for Medical Research.

SQUIBB®

© 1981 E.R. Squibb & Sons, Inc.

Issued: January 1981

(Continued from Page 18)

February 16-20—**Postgraduate Institute for Emergency Room Physicians, Symposium III.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $425.

March 8-14—**2nd Annual Mammoth Mountain Emergency Medicine Ski Conference.** UCI at Mammoth Mountain. One week. 25 hrs. $290. Contact: Daniel Abbott, MD, P.O. Box 52-B, Newport Beach 92662. (714) 642-7080.

March 16-20—**Postgraduate Institute for Emergency Room Physicians, Symposium II.** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $425.

April 18-25—**Emergency Medical Care.** Univ. of Washington School of Medicine at Wailea Beach, Maui. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

April 24-26—**Advanced Cardiac Life Support Workshops.** Emergency Medical Systems at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact. EMS, 2310 Mason St., San Francisco 94133. (415) 956-5900.

April 25-May 2—**Emergency Medicine.** USC at Royal Lahaina Hotel, Maui. One week. $350.

April 27-May 1—**Advanced Problems in Cardiac Emergencies.** UCSD at Kauai, Hawaii. Monday-Friday. 21 hrs. $325.

May 4-8—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $425.

May 7-9—**Cardiovascular Emergencies.** See Medicine, May 7-9.

May 13—**Emergency Medicine.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6 hrs. $35. Contact: Cont. Med. Ed., N. T. Enloe Mem. Hosp., 5th Ave. and The Esplanade, Chico 95926. (800) 822-8102, ext. 7375.

May 25-26—**Advanced Cardiac Life Support.** Emergency Care Education Center at Queen Mary, Long Beach. Monday-Tuesday. 12 hrs. $130. Contact: ECEC, P.O. Box 9639, Marina Del Rey 90291. (213) 822-1312.

May 26-30—**California Chapter, American College of Emergency Physicians—10th Annual Scientific Assembly.** Hyatt on Union Square, San Francisco. Tuesday-Saturday. Contact: Calif. Chap., ACEP, 6839 Lincoln Blvd., Suite 240, Los Angeles 90045.

June 1-5—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

June 15-19—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $425.

July 24-26—**Advanced Cardiac Life Support Workshops.** Emergency Medical Systems at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact. EMS, 2310 Mason St., San Francisco 94133. (415) 956-5900.

July 27-28—**Advanced Cardiac Life Support.** Emergency Care Education Center at Queen Mary, Long Beach. Monday-Tuesday. 12 hrs. $130. Contact: ECEC, P.O. Box 9639, Marina Del Rey 90291. (213) 822-1312.

August 3-7—**Postgraduate Institute for Emergency Room Physicians, Symposium II.** UCSD. Monday-Friday. 40 hrs. $425.

Emergency Medicine Grand Rounds. Herrick Hospital and Health Center, Berkeley. 2nd Wednesday of each month; 12:00-1:00 p.m. Cat. I—CMA, AMA, ACEP. Free, including lunch. Contact: James Simon, MD, Emergency Med. Dept., Herrick Hosp. and Health Ctr., 2001 Dwight Way, Berkeley 94705. (415) 540-4555.

MEDICINE

February 16-18—**Recent Advances in Clinical Endocrinology.** UCSF at Sir Francis Drake Hotel, San Francisco. Monday-Wednesday.

February 17-20—**Epilepsy in Childhood and Adolescence—32nd Annual Western Institute on Epilepsy.** Univ. of Nevada School of Medicine, Reno. Tuesday-Friday. Contact: Cont. Med. Ed., College Inn, Univ. of Nevada, Reno 89557.

February 18-20—**Neuro-Orthopedic Screening.** UCSD at Vacation Village, San Diego. Wednesday-Friday.

February 18-April 22—**Gastroenterology.** UCLA. Wednesday evenings.

February 19-22—**Federation of Western Societies of Neurological Science.** Stanford Court, San Francisco. Thursday-Sunday. Contact: Grant E. Gauger, MD, 1411 E. 31st St., Oakland 94602.

February 19-23—**Sacramento Valley Dermatological Society—Annual Winter Seminar.** North Lake Tahoe. Thursday-Monday. 20 hrs. Contact: Sacramento Valley Dermatological Society, c/o Dr. Bock, 1502 St. Marks Plaza, Stockton 95207.

February 20-22—**Pathophysiology and Techniques of Cardiopulmonary Bypass.** Cardiothoracic Research and Education Fndn., American Heart Assn., American Lung Assn., Nat'l Critical Care Institute of Education, Vascular Disease Fndn. at Mission Bay Hilton, San Diego. Friday-Sunday. $250. Contact: CREF, P.O. Box 33185, San Diego 92103.

February 21—**Workshop in Advanced Electrocardiography.** PMC. Saturday. 7 hrs. $110.

February 21-28—**Metabolism and Endocrinology.** Univ. of Washington School of Medicine at Kona Surf Hotel, Kona, Hawaii. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

February 21-28—**Practical Neurology.** Univ. of Washington School of Medicine at Ilikai Hotel, Honolulu. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

February 23-26—**Advances in Clinical Practice of Hematology/Oncology.** Scripps Clinic and Research Fndn. at Vacation Village, San Diego. Monday-Thursday. 25 hrs. $290. Contact: Nomi Feldman, 2321 Morena Blvd., San Diego 92110. (714) 275-0650.

February 25—**Hospital Acquired Infections.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday. 7½ hrs. Contact: Program Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

February 27-March 1—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Sahara Hotel, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

February 28—**21st Annual Scientific Symposium on Kidney Disease.** Kidney Foundation of Southern Calif. at Ambassador Hotel, Los Angeles. Saturday. $90. Contact: Kidney Fndn. of So. Calif., 6820 Tijera Blvd., Suite 111, Los Angeles 90045. (213) 641-8152.

March 2-4—**Dermatology for Primary Care Physicians.** UCSD at Hilton, San Diego. Monday-Wednesday. 12 hrs. $175.

March 2-4—**Immunology.** STAN. Monday-Wednesday. 13 hrs. $225.

March 2-4—**Dermatologic Problems of Interest to Internists.** STAN at Marriott's Rancho Las Palmas Resort, Rancho Mirage. Monday-Wednesday. 15 hrs. $200.

March 2-4—**Basic Neuroscience.** STAN.

March 4-7—**Immunology and Clinical Practice of Allergy—5th Annual Course.** UCSD at Hilton, San Diego. Thursday-Saturday. 20 hrs.

March 7-11—**American Academy of Allergy.** Hilton Hotel, San Francisco. Saturday-Wednesday. 32 hrs. $125, nonmembers. Contact: Donald McNeil, Exec. Dir., AAA, 611 E. Wells St., Milwaukee, WI 53202. (414) 272-6071.

March 8-11—**Consultants' Course in Dermatology.** UCSF at Ahwahnee Hotel, Yosemite. Sunday-Wednesday.

March 11—**Common Fractures and Joint Injuries.** LLU. Wednesday. 4 hrs. $30.

(Continued on Page 27)

When she can't manage, you can.

The sweats. The hot flushes. The distress and discomfort of atrophic vaginitis. The possibility of osteoporosis.* The menopause.

For many women, it's a time of confusion and frustration. Counseling can help her overcome these feelings. But counseling *can't* stop vasomotor and vaginal symptoms, or retard bone loss*...the true signs of estrogen deficiency. And that's where she needs you most.

You're an expert at estrogen replacement. You know why it should be used. When it's best avoided. How to cycle therapy. Determine dosage. Check for contraindications and possible complications. Follow-up. You know when therapy should begin, and when it deserves to end.

Most of all, you know your patient—and when she needs the effective relief you can give her with PREMARIN.

When it comes to managing the estrogen-deficiency symptoms of the menopause, you've got what it takes.

*Conjugated Estrogens Tablets have been evaluated as probably effective for postmenopausal osteoporosis

Prescribed with care by physicians who care.

PREMARIN®
BRAND OF
CONJUGATED ESTROGENS TABLETS, U.S.P.
0.3 mg/0.625 mg/1.25 mg/2.5 mg

Please see following page for brief summary of prescribing information.

BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION, SEE PACKAGE CIRCULAR)

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA

Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year.[1-3] This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade.[4] The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment[1] and on estrogen dose.[3] In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration,[3] it therefore appears prudent to utilize such a regimen. Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY

The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare.[5,6] This risk has been estimated as not greater than 4 per 1000 exposures.[7] Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis,[8-12] epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes. Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects.[13-16] One case control study[16] estimated a 4.7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses. If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

DESCRIPTION: PREMARIN (Conjugated Estrogens Tablets, U.S.P.) for oral administration contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters.

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications for use as follows:

Effective:

1. Moderate to severe *vasomotor* symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions.)
2. Atrophic vaginitis.
3. Kraurosis vulvae.
4. Female hypogonadism.
5. Female castration.
6. Primary ovarian failure.
7. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.
8. Prostatic carcinoma—palliative therapy of advanced disease.
9. Postpartum breast engorgement—Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy. Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens.[19]

PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions: 1. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease. 2. Known or suspected estrogen-dependent neoplasia. 3. Known or suspected pregnancy. (See Boxed Warning). 4. Undiagnosed abnormal genital bleeding. 5. Active thrombophlebitis or thromboembolic disorders. 6. A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).

WARNINGS: At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast,[17] although a recent study has raised this possibility.[18] There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms. A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens.[17]

Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement, it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement.[19-22] Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction.[23-30] Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users.[31,32] An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives.[33,34] If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization. Estrogens should not be used in persons with active thrombophlebitis, thromboembolic disorders, or in persons with a history of such disorders in association with estrogen use. They should be used with caution in patients with cerebral vascular or coronary artery disease. Large doses (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown[35] to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. When doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a clear risk.

Benign hepatic adenomas should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives.[36] Increased blood pressure may occur with use of estrogens in the menopause[37] and blood pressure should be monitored with estrogen use. A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed. Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed. Conditions influenced by fluid retention such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc. Oral contraceptives appear to be associated with an increased incidence of mental depression.[23a] Patients with a history of depression should be carefully observed. Preexisting uterine leiomyomata may increase in size during estrogen use. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated. Estrogens should be used with care in patients with impaired liver function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete.

The following changes may be expected with larger doses of estrogen.

a. Increased sulfobromophthalein retention.

b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.

d. Impaired glucose tolerance.

e. Decreased pregnanediol excretion.

f. Reduced response to metyrapone test.

g. Reduced serum folate concentration.

h. Increased serum triglyceride and phospholipid concentration.

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives: breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhea; premenstrual-like syndrome, amenorrhea during and after treatment, increase in size of uterine fibromyomata, vaginal candidiasis, change in cervical erosion and in degree of cervical secretion; cystitis-like syndrome, tenderness, enlargement, secretion (of breasts), nausea, vomiting, abdominal cramps, bloating, cholestatic jaundice, chloasma or melasma which may persist when drug is discontinued, erythema multiforme, erythema nodosum, hemorrhagic eruption; loss of scalp hair, hirsutism; steepening of corneal curvature; intolerance to contact lenses; headache, migraine, dizziness, mental depression; chorea, increase or decrease in weight; reduced carbohydrate tolerance, aggravation of porphyria; edema; changes in libido.

ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION: 1. *Given cyclically for short term use only.* For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0.3 to 1.25 mg or more daily).

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (*e.g.*, three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

2. *Given cyclically:* Female hypogonadism. Female castration. Primary ovarian failure. Osteoporosis.

Female hypogonadism—2.5 to 7.5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration. If bleeding does not occur by the end of this period, the same dosage schedule is repeated. The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium.

If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U.S.P.), 2.5 to 7.5 mg daily in divided doses, for 20 days. During the last five days of estrogen therapy, give an oral progestin. If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding.

Female castration and primary ovarian failure—1.25 mg daily, cyclically. Adjust upward or downward according to response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

Osteoporosis (to retard progression)—1.25 mg daily, cyclically.

3. *Given for a few days.* Prevention of postpartum breast engorgement—3.75 mg every four hours for five doses, or 1.25 mg every four hours for five days.

4. *Given chronically:* Inoperable progressing prostatic cancer—1.25 to 2.5 mg three times daily.

Inoperable progressing breast cancer in appropriately selected men and postmenopausal women—10 mg three times daily for a period of at least three months.

Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U.S.P.) No. 865—Each *purple* tablet contains 2.5 mg in bottles of 100 and 1,000. No. 866—Each *yellow* tablet contains 1.25 mg in bottles of 100 and 1,000. Also in unit dose package of 100. No. 867—Each *red* tablet contains 0.625 mg in bottles of 100 and 1,000. Also in unit dose package of 100. No. 868—Each *green* tablet contains 0.3 mg in bottles of 100 and 1,000.

PHYSICIAN REFERENCES: 1. Ziel, H.K., *et al.*: N. Engl. J. Med. *293*:1167-1170, 1975. 2. Smith, D.C., *et al.*: N. Engl. J. Med. *293*:1164-1167, 1975. 3. Mack, T.M., *et al.*: N. Engl. J. Med. *294*:1262-1267, 1976. 4. Weiss, N.S., *et al.*: N. Engl. J. Med. *294*:1259-1262, 1976. 5. Herbst, A.L., *et al.*: N. Engl. J. Med. *284*:878-881, 1971. 6. Greenwald, P., *et al.*: N. Engl. J. Med. *285*:390-392, 1971. 7. Lanier, A., *et al.*: Mayo Clin. Proc. *48*:793-799, 1973. 8. Herbst, A., *et al.*: Obstet. Gynecol. *40*:287-298, 1972. 9. Herbst, A., *et al.*: Am. J. Obstet. Gynecol. *118*:607-615, 1974. 10. Herbst, A., *et al.*: N. Engl. J. Med. *292*:334-339, 1975. 11. Staff, A., *et al.*: Obstet. Gynecol. *43*:118-128, 1974. 12. Sherman, A.I., *et al.*: Obstet. Gynecol. *44*:531-545, 1974. 13. Gal, I., *et al.*: Nature *216*:83, 1967. 14. Levy, E.P., *et al.*: Lancet *1*:611, 1973. 15. Nora, J., *et al.*: Lancet *1*:941-942, 1973. 16. Janerich, D.T., *et al.*: N. Engl. J. Med. *291*:697-700, 1974. 17. Boston Collaborative Drug Surveillance Program: N. Engl. J. Med. *290*:15-19, 1974. 18. Hoover, R., *et al.*: N. Engl. J. Med. *295*:401-405, 1976. 19. Daniel, D.G., *et al.*: Lancet *2*:287-289, 1967. 20. The Veterans Administration Cooperative Urological Research Group: J. Urol. *98*:516-522, 1967. 21. Bailar, J.C.: Lancet *2*:560, 1967. 22. Blackard, C., *et al.*: Cancer *26*:249-256, 1970. 23. Royal College of General Practitioners: J. R. Coll. Gen. Pract. *13*:267-279, 1967. 23a. Royal College of General Practitioners: Oral Contraceptives and Health, New York, Pitman Corp., 1974. 24. Inman, W.H.W., *et al.*: Br. Med. J. *2*:193-199, 1968. 25. Vessey, M.P., *et al.*: Br. Med. J. *2*:651-657, 1969. 26. Sartwell, P.E., *et al.*: Am. J. Epidemiol. *90*:365-380, 1969. 27. Collaborative Group for the Study of Stroke in Young Women: N. Engl. J. Med. *288*:871-878, 1973. 28. Collaborative Group for the Study of Stroke in Young Women: J.A.M.A. *231*:718-722, 1975. 29. Mann, J.I., *et al.*: Br. Med. J. *2*:245-248, 1975. 30. Mann, J.I., *et al.*: Br. Med. J. *2*:241-245, 1975. 31. Inman, W.H.W., *et al.*: Br. Med. J. *2*:203-209, 1970. 32. Stolley, P.D., *et al.*: Am. J. Epidemiol. *102*:197-208, 1975. 33. Vessey, M.P., *et al.*: Br. Med. J. *3*:123-126, 1970. 34. Greene, G.R., *et al.*: Am. J. Public Health *62*:680-685, 1972. 35. Coronary Drug Project Research Group: J.A.M.A. *214*:1303-1313, 1970. 36. Mays, E.T., *et al.*: J.A.M.A. *235*:730-732, 1976. 37. Pfeffer, R.I., *et al.*: Am. J. Epidemiol. *103*:445-456, 1976.

7457/181

Ayerst® AYERST LABORATORIES
New York, N.Y. 10017

(Continued from Page 23)

March 13-14—**Cardiac Ischemia and Arrhythmias—Current Concepts for Diagnosis and Treatment.** International Medical Education Corp. at Sheraton Fisherman's Wharf, San Francisco. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

March 13-14—**Diagnosis and Treatment of Venous Thromboembolism.** PMC. Friday-Saturday. 10 hrs. $125.

March 15-18—**Symposium on Gastroenterology.** UCSF at Ahwahnee Hotel, Yosemite. Sunday-Wednesday.

March 15-19—**American College of Cardiology.** San Francisco. Sunday-Thursday. Contact: ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

March 23-April 4—**Intensive Review of Internal Medicine—29th Annual.** USC. Two weeks.

March 27-29—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Aladdin Hotel, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

March 29-April 1—**Basic Cardiology for the Practicing Physician.** UCSF at Hyatt, Lake Tahoe. Sunday-Wednesday. 13 hrs. $175.

April 2-3—**Gastroenterology for the Practicing Internist.** UCLA at Palm Springs. Thursday-Friday.

April 4-5—**Infectious Disease for the Practicing Internist.** UCLA at Palm Springs. Saturday-Sunday.

April 5-8—**Cosmetics for the Clinician: A Symposium for Dermatologists.** UCD at Ahwahnee Hotel, Yosemite. Sunday-Wednesday.

April 6-15—**Cardiology for the Consultant: A Clinician's Retreat.** American College of Cardiology at Rancho Santa Fe. 10 days. Contact: Registration Sec., Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

April 8—**Cardiology Symposium.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6 hrs. $35. Contact: Cont. Med. Ed., N. T. Enloe Memorial Hosp., 5th Ave and The Esplanade, Chico 95926. (800) 822-8102, ext. 7375.

April 8—**Annual Physicians' Cardiovascular Symposium.** American Heart Assn., Central Valley Chapter, at Hilton, Fresno. Wednesday. Contact: Genny Berry, AHA, Central Valley Chap., 3835 N. West Ave., Fresno 93705. (209) 224-8215.

April 8-10—**Update in Pediatric Pulmonary and Intensive Care.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. Contact: Prog. Coordinator, Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

April 8-11—**California Blood Bank System—29th Annual Meeting.** Hyatt Airport Hotel, Los Angeles. Wednesday-Saturday. Contact: Mrs. Beverley Hayhurst, Exec. Sec., CBBS, P.O. Box 5401, San Bernardino 92412. (714) 885-6503.

April 10—**22nd Annual Physicians' Symposium: Hearts, Hypertension and Health.** American Heart Assn., Santa Clara County Chap., at LeBaron Hotel, San Jose. Friday. 6 hrs. $35. Contact: Harriet M. Schutte, RN, PhD, AHA, Santa Clara Co. Chap., 3003 Moorpark Ave., San Jose 95128. (408) 247-8555.

April 10-12—**Cardiac Ischemia and Arrhythmias—Current Concepts for Diagnosis and Treatment.** International Medical Education Corp at Sheraton, Anaheim. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

May 1-2—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Sheraton Fisherman's Wharf, San Francisco. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

May 2-3—**Practical Dermatology.** UCLA at Hotel Biltmore, Santa Barbara. Saturday-Sunday.

May 6—**Respiratory.** St. Francis Medical Center, Lynwood. Wednesday. 6 hrs. Contact: Allan M. Hoffman, EdD, Dir. of Med. Ed., St. Francis Med. Ctr., 3630 Imperial Highway, Lynwood 90262. (213) 603-6174.

May 6—**Thyroid '81.** Hospital of the Good Samaritan at Bonaventure Hotel, Los Angeles. Wednesday. 7 hrs. Contact: Mary Jane Thompson, Hosp. of the Good Samaritan, 616 S. Witmer St., Los Angeles 90017. (213) 488-8908.

May 6—**Young Investigators Forum.** American Heart Assn.-Greater Los Angeles Affiliate at UCLA. Wednesday. 6 hrs. Contact: LaVerna M. Titus, AHA-GLAA, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

May 7-9—**Cardiovascular Emergencies.** American College of Cardiology and PMC at Mark Hopkins Hotel, San Francisco. Thursday-Saturday. 18 hrs. Contact: Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

May 8-10—**Cardiac Ischemia and Arrhythmias—Current Concepts for Diagnosis and Treatment.** International Medical Education Corp. at Sahara Hotel, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

May 18-21—**Endocrinology for the Practicing Physician.** LLU at Mauna Kea Beach Hotel, Kamuela, Hawaii. Monday-Thursday. 16 hrs. $200.

May 18-22—**Advances in Internal Medicine.** UCSF at Hyatt on Union Square, San Francisco. Monday-Friday.

May 23-30—**Allergy and Immunology.** Univ. of Washington School of Medicine at Wailea Beach, Maui, Hawaii. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle 98195.

May 31-June 4—**Internal Medicine for the Generalist—1981.** UCSD at Hilton, San Diego. Sunday-Thursday. 23 hrs.

June 1-5—**Advances in Internal Medicine.** UCSF. Monday-Friday.

June 3—**Gastroenterology.** St. Francis Medical Center, Lynwood. Wednesday. 6 hrs. Contact: Allan M. Hoffman, EdD, Dir. of Med. Ed., St. Francis Med. Ctr., 3630 Imperial Highway, Lynwood 90262. (213) 603-6174.

June 12-14—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Sahara Hotel, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

June 26-28—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Sheraton, Anaheim. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

July 13-17—**Third International Psoriasis Symposium.** STAN. Monday-Friday.

July 18-25—**Cardiovascular Medicine and Surgery: An Advanced Course.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 23 hrs. $295.

August 7-8—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Doubletree Inn, Monterey. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

August 21-22—**Cardiac Rehabilitation.** International Medical Education Corp. at Sheraton, Anaheim. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

OBSTETRICS AND GYNECOLOGY

April 4-11—**Current Concepts in Ob/Gyn.** Univ. of Washington School of Medicine at Kona Surf Hotel, Kona, Hawaii. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

(Continued on Page 39)

High intensit
the ke

Trimpex (trimethoprim/Roche) diffuses and concentrates

Trimpex achieves high intensity concentrations in the urine—significantly greater levels than the MICs of susceptible urinary pathogens—a major reason for Trimpex high performance. Trimpex also diffuses into vaginal fluid at concentrations that inhibit coliform colonization of the vaginal introitus.

ROCHE®

oncentrations—
o high performance

% overall efficacy

controlled, comparative multiclinic studies, methoprim delivered a 95% overall cure te (127 of 133 patients) seven days after mpletion of therapy.† The most common usative uropathogens were *E. coli, Klebsiella neumoniae, Proteus mirabilis* and *nterobacter* species.

e effects generally infrequent nd mild

recommended dosage, the incidence of skin sh has been only 2.9%, with no reported cidence of diarrhea. In clinical studies hich employed higher doses of Trimpex rimethoprim/Roche), an elevated incidence of sh was noted. (See Adverse Reactions section product summary.)

ety considerations

impex is contraindicated in patients persensitive to the drug and in patients with ocumented megaloblastic anemia due to folate deficiency. The benefits of Trimpex therapy during pregnancy and the nursing period should be weighed against the risks. Safe use in infants under 2 months and effectiveness in children under 12 years of age have not been established. (For further discussion of use in pregnancy, and other safety considerations, please see product summary on the following page of this advertisement.)

One small tablet B.I.D.—and it's economical

The convenient Trimpex dosage schedule—one small tablet twice a day for 10 days—is easier to follow than the Q.I.D. regimens of other agents. And Trimpex costs less than nitrofurantoin macrocrystals or any cephalosporin.

Performance • Convenience • Economy •
Three good reasons to prescribe Trimpex for initial uncomplicated urinary tract infections.

ta on file, Hoffmann-La Roche Inc.

95% EFFICACY WITH ONE SMALL TABLET TWICE A DAY.

Trimpex® 100-mg scored tablets
trimethoprim/ROCHE

FOR INITIAL EPISODES OF UNCOMPLICATED URINARY TRACT INFECTIONS*

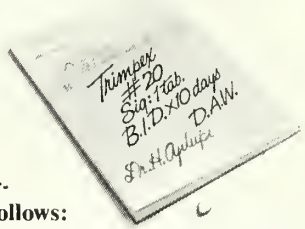
*due to susceptible strains of common uropathogens.

Before prescribing, please consult summary of product information on the following page.

95% efficacy with one small tablet twice a day

Trimpex®
trimethoprim/ROCHE

Diffuses and concentrates



Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS AND USE: For treatment of initial episodes of uncomplicated urinary tract infections due to susceptible strains of: *Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae* and *Enterobacter* species. Perform culture and susceptibility tests to determine bacterial susceptibility to trimethoprim. Therapy may be initiated prior to obtaining test results.

CONTRAINDICATIONS: Hypersensitivity to trimethoprim and in those with documented megaloblastic anemia due to folate deficiency.

WARNINGS: Occasional interference with hematopoiesis, especially when administered in large doses and/or for prolonged periods. Obtain CBC if early indications of serious blood disorders are noted; *i.e.*, sore throat, fever, pallor or purpura. Discontinue therapy if the count of any formed blood element is significantly reduced.

PRECAUTIONS: *General:* Give cautiously to patients with possible folate deficiency or those with impaired renal or hepatic function. Folates may be administered concomitantly without interfering with trimethoprim's antimicrobial action.

PREGNANCY

Category C: Because it may interfere with folic acid metabolism, use only during pregnancy if potential benefits justify the potential risk to the fetus.

Nursing Mothers: Because trimethoprim is excreted in human milk and may interfere with folic acid metabolism, exercise caution when administering Trimpex. *Pediatric Use:* Safety has not been demonstrated in infants under two months of age. Effectiveness not established in children under the age of 12.

ADVERSE REACTIONS: *Dermatologic Reactions:* Rash, pruritus and exfoliative dermatitis. At the recommended dose of 100 mg b.i.d., the incidence of rash is 2.9%. In clinical studies using high doses of Trimpex, a greater incidence of maculopapular, morbilliform, pruritic and generally mild to moderate rash was noted, appearing 7 to 14 days after therapy was initiated. *Gastrointestinal Reactions:* Epigastric distress, nausea, vomiting and glossitis. *Hematologic Reactions:* Thrombocytopenia, leukopenia, neutropenia, megaloblastic anemia and methemoglobinemia. *Miscellaneous Reactions:* Fever, elevation of serum transaminase and bilirubin, and increased BUN and serum creatinine levels.

DOSAGE AND ADMINISTRATION: Usual oral adult dosage: 100 mg Trimpex every 12 hours for 10 days.

In patients with a creatinine clearance of less than 15 ml/min, trimethoprim is not recommended. If creatinine clearance is between 15 to 30 ml/min, the dose should be 50 mg every 12 hours.

Effectiveness not established in children under the age of 12.

HOW SUPPLIED: Tablets, each containing 100 mg trimethoprim—bottles of 100; Tel-E-Dose® package of 100; Prescription Paks of 20.

ROCHE® LABORATORIES
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

DOCTORS' SPECIAL!

Give your family a

Condo Vacation in Hawaii

and we'll give you use of a

Car FREE!

When you stay in a 1-bedroom oceanview or 2-bedroom condominium in one of these luxurious resorts, you'll have the use of a car free. All condominiums are on or near the beach and have daily maid service.

WAIKIKI
Island Colony or Waikiki Sunset
Pool, golf nearby and many luxury extras. From $59/day-$370/week
1-4 persons

MAUI
Kaanapali Shores
Free tennis, pool, golf nearby. From $78/day-$490/week
1-4 persons

HAWAII
Kona Lagoon
Free tennis, golf nearby. From $85/day-$535/week
1-4 persons

KAUAI
Pono Kai
Mile-long beach, free tennis, barbecue area, sauna. From $58/day-$365/week
1-4 persons

Serving Hawaii Visitors for More Than 30 Years

hcp HCP Condo Resorts

Andre S. Tarlbouet, President
2299 Kuhio Avenue, Honolulu, Hawaii 96815

For reservations, beautiful four-color brochures or information about any of HCP's 18 hotels and condominiums in Hawaii, see your travel agent or call Hawaii Toll Free 800-367-5124.

Call Hawaii Toll Free
800-367-5124

Read across specialty lines.

Each month the WESTERN JOURNAL provides an excellent, quick way
for busy physicians to keep abreast
of what is happening in other fields of medicine.
It seeks also to offer a balanced fare of scientific and social progress,
with something in every issue for students,
scholars, practitioners, academicians, researchers and Medicine's political leaders.

The WESTERN JOURNAL lets you read across specialty lines.

THE WESTERN
Journal of Medicine

Please mail this coupon with enclosed payment to:
THE WESTERN JOURNAL OF MEDICINE—Circulation Department
731 Market Street, San Francisco, California 94103

WJ2/81

Subscriptions, U.S. and Canada $10 All other countries $18

Enclosed is $_____ to cover _____ subscriptions. Subscription renewal ☐

Send subscription

TO: _____

_____
Street

_____
City State Zip

_____
Specialty

Gift Card to read "From _____"

Regular subscription ☐ Foreign subscription ☐

TO: _____

_____
Street

_____
City State Zip

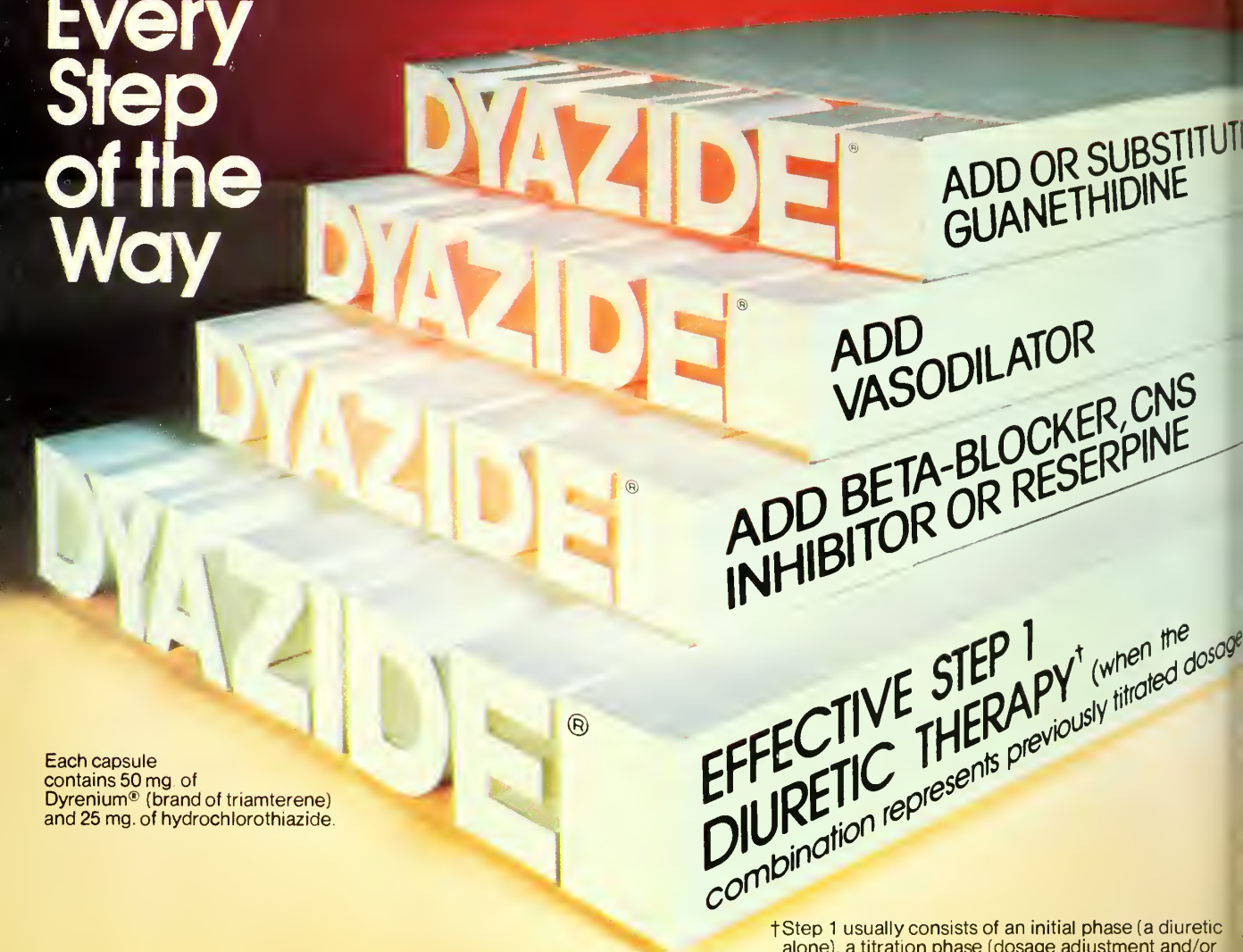
_____
Specialty

Gift Card to read "From _____"

Regular subscription ☐ Foreign subscription ☐

In Hypertension*...When You Need to Conserve K^+

Every Step of the Way



Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

†Step 1 usually consists of an initial phase (a diuretic alone), a titration phase (dosage adjustment and/or addition of a K^+ supplement or K^+-sparing agent and maintenance phase (a diuretic alone or in combination with a K^+ supplement or K^+-sparing agent).

Serum K^+ and BUN should be checked periodically (see Warnings).

Before prescribing, see complete prescribing information in SK&F Co. literature or *PDR*. A brief summary follows:

* **WARNING**
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K^+ frequently; both can cause K^+ retention and elevated serum K^+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in postsympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia, although uncommon, has been reported. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components.

Supplied: Bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

© SK&F Co., 1980

SK&F CO.
a SmithKline company
Carolina, P.R. 00630

THE WESTERN
Journal of Medicine

Refer to: Newton GW, Schmidt ES, Lewis JP, et al: Amygdalin toxicity studies in rats predict chronic cyanide poisoning in humans. West J Med 134:97-103, Feb 1981

Amygdalin Toxicity Studies in Rats Predict Chronic Cyanide Poisoning in Humans

GEORGE W. NEWTON, MA; ERIC S. SCHMIDT, BS; JERRY P. LEWIS, MD; ERIC CONN, PhD, *and* RUTH LAWRENCE, MD, *Davis, California*

Significant amounts of cyanide are released when amygdalin (Laetrile), a cyanogenic glycoside, is given orally or intravenously to rats. The amount of cyanide liberated following oral administration is dependent in part on the bacterial flora of the gut and can be suppressed by antibiotic pretreatment of the animals. Bacteria from human feces likewise hydrolyze amygdalin with release of cyanide. Humans taking amygdalin orally in the hope of preventing cancer are likely to be exposed to levels of cyanide in excess of that associated with the development of tropical ataxic neuropathy in people of underdeveloped countries where food containing cyanogenic glycosides is a staple part of the diet.

AMYGDALIN IS A cyanogenic glycoside found in apricot kernels, bitter almonds and seeds of other members of the genus *Prunus*.[1] It is commonly known as Laetrile, a drug that has been advocated variously as (1) a cure for all types of cancer, (2) a cure for some types of cancers, (3) a control for cancer with prolongation of life, (4) a useful drug to reduce the morbidity of cancer and its treatments, (5) a drug to offer some hope to terminally ill patients and (6) a drug to prevent cancer.[2] None of these claims can be substantiated. Throughout the barrage of pro-Laetrile propaganda, with its shifting emphasis from cure to control to prophylaxis, the proponents of Laetrile have staunchly claimed the drug itself is totally without toxicity, stating that "Laetrile is even less toxic than sugar."[3] Some states have passed laws legalizing this unproven cancer remedy, believing if it does no harm it should be available to cancer patients who have faith in it. The question of the fraudulent representation of Laetrile's efficacy and the diversion of cancer patients from an effective treatment to a worthless nostrum has often been overlooked.

To place amygdalin in its proper scientific setting, numerous animal studies have been reported showing the compound's lack of efficacy.[4] No

From the Department of Internal Medicine, Section of Hematology and Oncology (Messrs. Newton and Schmidt, Dr. Lewis), Section of Infectious and Immunologic Diseases (Dr. Lawrence), School of Medicine, and the Department of Biochemistry and Biophysics (Dr. Conn), College of Agriculture and Environmental Sciences, University of California, Davis. Dr. Lawrence is now affiliated with the Department of Medicine, Texas Technological University School of Medicine, Lubbock, Texas.

These studies were supported by a Developmental Research Grant from the American Cancer Society, #RD-49. Mr. Eric Schmidt's support was made possible by funds from Achievement Rewards for College Scientists Foundation, Inc. of San Francisco.

Submitted June 19, 1980.

Reprint requests to: Jerry P. Lewis, MD, Section of Hematology and Oncology, Department of Internal Medicine, 4301 X Street, Sacramento, CA 95817.

study has shown it to have therapeutic effects. Likewise, clinical studies in man have found no effect by amygdalin on cancer in humans.[4] On the other hand, amygdalin may be hazardous when administered to animals,[5,6] can be toxic when administered to humans,[4,7] has been lethal in at least three cases in humans[8-13] and has produced a near fatality in a child who was given a Laetrile enema.[14]

In an earlier study we showed that amygdalin fed to dogs produced cyanide toxicity in 100 percent of the animals when the compound was administered in conjunction with sweet almonds, a food containing β-glucosidase enzymes which hydrolyze amygdalin. The doses of amygdalin used in our studies were comparable on a gram per square meter basis with doses taken by humans.[5] In addition to signs of respiratory, cardiac and neurologic impairment, 60 percent of the dogs died of cyanide poisoning. These earlier studies focused on the acute toxicity of amygdalin; our current study addresses the potential for chronic cyanide toxicity from amygdalin.

Materials, Methods and Test Subjects

Drugs

Amygdalin for the LD_{50} (lethal dose for 50 percent survival of group) studies had been confiscated by the Fraud Division of the Department of Health, State of California. It had been manufactured in Munich, Germany, by SIDUS Arzneimittel GmbH and was labeled as "Amygdalin 2G for parenteral use." The Department of Health, State of California, had analyzed the drug and determined it was high-quality amygdalin without known impurities and contained 2.07 grams amygdalin per bottle. In subsequent studies following the LD_{50} determinations, we used crystalline amygdalin from Sigma Laboratories, St. Louis (99 percent pure). Both compounds were *(R)*-amygdalin. Neomycin sulfate (Mycrifradin) was obtained from Upjohn Pharmaceutical Company.

Experimental Animals

Female Fischer 344 rats were obtained from Simonsen Laboratories, Inc., Gilroy, California. These animals weighed between 150 and 200 grams when entered in the study. Animals were housed in pairs for the LD_{50} study and singly in metabolic cages for other experiments. The diet was similar to that used by others in investigating the effects of other cyanogenic glycosides in rats.[15] The diet did not contain β-glucosidase. We modified the diet used by Barrett and co-workers such that it was barely sufficient in methionine (0.01 percent rather than 0.3 percent), because excess sulfur from methionine might have altered the LD_{50} data and because this dietary modification closely mimics the meat-free diet advocated by proponents of Laetrile. We found this level of methionine (which perhaps is the most important amino acid that serves as a donor of sulfur for thiocyanate production) to be the lowest compatible with normal growth.

LD_{50} Studies of Amygdalin

We first determined the oral dose of amygdalin that was lethal to 50 percent of our rats (that is, LD_{50}). This study was necessary to be certain that our subsequent investigations would be carried out with minimal loss of animals.*

The LD_{50} dose of orally administered amygdalin was determined in a series of five experiments, each utilizing 60 rats. Amygdalin was introduced via gastric tube to rats lightly anesthetized with ether. This level of anesthesia permitted the rats to recover in five minutes. In the last two experiments a small amount of blue food coloring was added to the amygdalin as a tracer. The gastrointestinal tracts of these latter animals were examined after death to assess how far the drug had passed down the alimentary tract. All rats were observed for six hours and then followed daily for 14 days. Doses of amygdalin ranged from below 400 mg per kg of body weight to above 1,100 mg per kg of body weight. Blood specimens were collected at the time of death by intracardiac puncture and immediately frozen for blood cyanide determinations. Whole blood cyanide determinations were done according to the technique of Rieders.[16]

Kinetic Studies of Amygdalin

Urinary amygdalin and thiocyanate excretion following the oral administration of the drug was investigated in 20 rats. These studies, which were replicated once, were designed to document the effect of orally administered amygdalin on cyanide release and excretion of amygdalin. In these studies the rats were housed individually in metabolic cages. Again, the rats had free access to a balanced diet marginally sufficient in methionine.

*Mr. David Lewis assisted in carrying out the LD_{50} studies.

The animals were divided into two groups. After 10 to 15 days of subsistence on the controlled diet, half received 1 ml containing 12 mg of neomycin via gastric tube followed on the subsequent three days by 1 ml containing 9 mg of neomycin. Rats not given the antibiotic received 1 ml of distilled water on each of these days by gastric tube. The antibiotic was well tolerated by the rats and did not produce diarrhea. Urine was collected from all study rats at 24-hour intervals.

The day following the last dose of neomycin or distilled water, amygdalin in a concentration of 250 mg per kg of body weight (approximately an LD_{10} dose) was administered orally to the rats. Urine was collected from each rat daily and frozen until assayed for amygdalin and thiocyanate by technique of Ames (Flora, Cradock and Ames[17]) and a modified Lambert[18] method, respectively. Amygdalin, when hydrolyzed, is broken down to benzaldehyde, cyanide and two glucose molecules. The technique of Ames measures benzaldehyde. Cyanide is detoxified primarily by conversion to thiocyanate which is then excreted in the urine.

In a similar fashion, the urinary amygdalin and thiocyanate excretion following the intravenous administration of the drug was carried out.

Hydrolysis of Amygdalin, In Vitro Studies

The ability of various segments of the rat gastrointestinal tract to hydrolyze amygdalin was studied by incubating portions of the tract and its fecal contents with amygdalin and measuring cyanide generation.

To ascertain whether human fecal flora were also capable of hydrolyzing amygdalin, we tested the ability of certain common human fecal bacteria to hydrolyze amygdalin using purine cultures of *Escherichia coli, Bacteroides fragilis, Enterobacter aerogenes, Streptococcus fecalis* and *Clostridium perfringens*. Each organism was incubated overnight in thioglycolate broth medium supplemented with vitamin K and hemin. The final culture was adjusted to yield bacterial counts of 10^9 per ml. Cell-free culture filtrates of each culture were prepared by passage through a 0.4 μ Millipore filter. Both the broth cultures and the cell-free culture filtrates were incubated with amygdalin and the release of cyanide measured. To further explore the possibility of amygdalin hydrolysis by human fecal material, approximately 1 gram of fresh human feces was incubated with 1 mg of amygdalin, and hydrolysis of amygdalin with the release of cyanide was determined

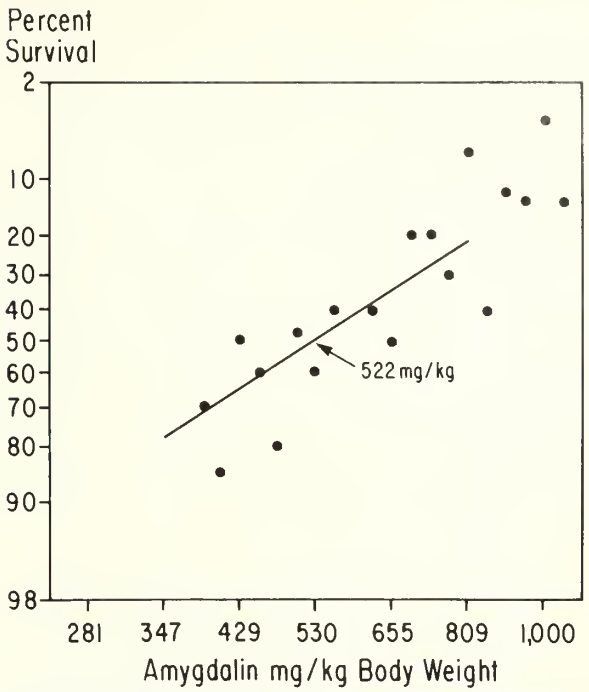


Figure 1.—Survival data of rats administered amygdalin orally. The 50 percent lethal dose (LD_{50}) in these studies is 522 mg per kg of body weight. Each dot represents the results in 5 to 20 rats. A lower number of animals per dose was used at the extremities of the range, a higher number of animals per dose was used in the midportion of the survival curve.

The ability of human gastric juice to hydrolyze amygdalin was investigated using 10 specimens of gastric juice with pH's ranging from 2.2 to 6.8. Gastric aspirate specimens were collected from patients undergoing gastric analysis at the University Medical Center, Sacramento, for diagnostic purposes and were made available for our studies by Dr. Lee Chen. The specimens were centrifuged at 5,000 rpm for five minutes to remove particulates, 1 ml supernatant was removed, added to 1 ml solution of 4 mM amygdalin and incubated at 37°C for one hour. Any cyanide released was captured in a 0.1 M sodium hydroxide solution. Analysis of the sodium hydroxide trap solution was carried out according to the Lambert method.[18]

Results

LD_{50} Studies

The results of the LD_{50} study are shown in Figure 1. Although great variability exists between groups of rats, we calculate the LD_{50} of amygdalin to be approximately 522 mg per kg of body weight. The first sign of neurologic damage appeared 80 minutes after administration of amyg-

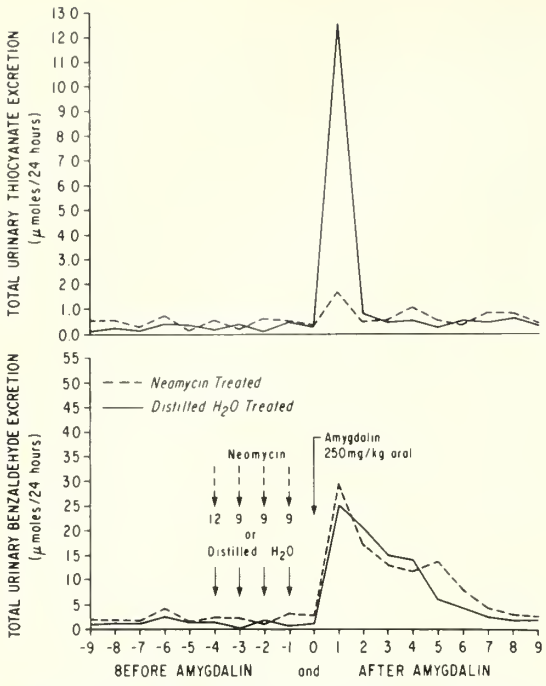


Figure 2.—Twenty-four hour urinary clearance of thiocyanate **(top panel)** and benzaldehyde **(lower panel)** before and after the oral administration of amygdalin. One standard error of the mean at all points on this figure is equal to or less than 8 percent.

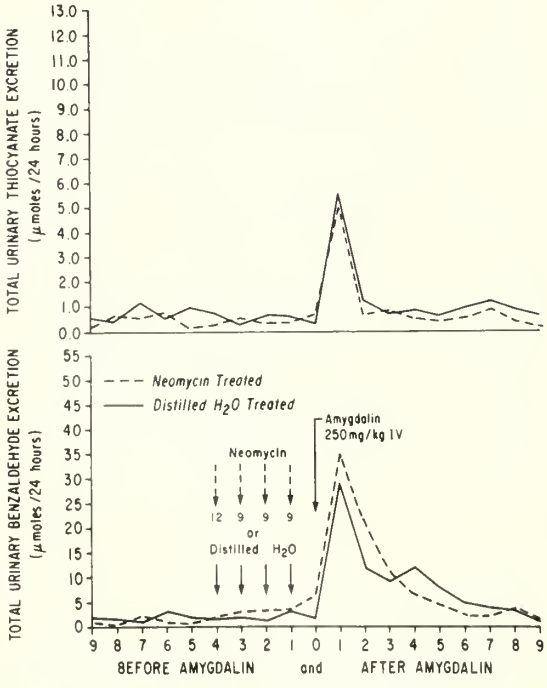


Figure 3.—Twenty-four hour urinary clearance of thiocyanate **(top panel)** and benzaldehyde **(lower panel)** before and after the intravenous administration of amygdalin. One standard error of the mean at all points on this figure is equal to or less than 5 percent.

dalin and was exemplified by hind-quarter ataxia. For those animals that progressed to death, ataxia increased until the rats were unable to right themselves. The rats' noses and paws then became cyanotic, the animals had labored respirations, urinated and defecated, lapsed into coma, convulsed and died. Autopsy of those animals given blue coloring showed the dye confined to the stomach with the exception of two animals in which the dye had extended into the duodenum.

There was no linear correlation between the amount of amygdalin administered and the blood cyanide level in those animals that died; however, all blood specimens assayed were either in the range of toxicity (greater than 50 μg per dl) or lethality (greater than 100 μg per dl).[16] Cyanide levels in blood specimens from 57 deceased animals ranged from 64.8 μg per dl to 425 μg per dl. This compares favorably with blood cyanide levels reported in rats that died following the intraperitoneal administration of amygdalin.[6]

Kinetic Studies of Amygdalin

The pattern of excretion of thiocyanate and amygdalin (expressed as benzaldehyde) following the oral administration of the drug is shown in Figure 2. The excretion of thiocyanate was greatly dependent upon whether or not the rats had previously been given neomycin. There was a minimal rise in urinary thiocyanate in those rats receiving neomycin and a 40-fold rise in those not receiving the antibiotic.

The data from rats given amygdalin intravenously are shown in Figure 3. There was a pronounced rise in 24-hour urine output of thiocyanate following intravenously given doses, and this result was independent of pretreatment of the animals with neomycin, suggesting that neomycin had no effect on cyanide release in those animals given the intravenous preparation. Following intravenous dosing, approximately 6 percent of the available cyanide from amygdalin was released. This is roughly 50 percent of that which is released following the oral administration of amygdalin in rats not previously given neomycin. The urinary amygdalin excretion continued for five to seven days and did not depend upon the route of amygdalin administration or the pretreatment of animals with neomycin. In these studies we accounted for 70 percent to 85 percent of the amygdalin injected as either amygdalin cleared through the kidneys or amygdalin hydrolyzed to cyanide and subsequently converted to thiocyanate before

renal clearance. Following the oral administration of amygdalin, we accounted for 89 percent to 97 percent of amygdalin.

Hydrolysis of Amygdalin, In Vitro Studies

Results of these studies are shown in Table 1. We found that all segments of rat gut tested were capable of hydrolyzing some amygdalin. Our in vivo studies show that this hydrolysis is blocked partially by neomycin. Therefore, it is quite likely that hydrolysis is accomplished primarily by bacterial action. The fact that hydrolysis occurred even in the gastric segment is compatible with our findings with the marker dye in our LD_{50} studies in which there was sufficient cyanide released while the drug was in the stomach to cause cyanide toxicity, including death.

As shown in Table 1, four of the bacterial species found in human feces were capable of hydrolyzing amygdalin; the most efficient bacteria in this regard were *Bacteroides fragilis,* a major constituent of human stool. On the other hand, cell-free filtrates of the broth cultures failed to hydrolyze amygdalin. Not shown in Table 1 is the fact that on incubating amygdalin with approximately 1 gram of human feces, 53 percent of the available hydrocyanic acid was released by hydrolysis.

The results of the human gastric acid studies are also given in Table 1 and show that no cyanide was released in acid gastric juice, but as the pH rises above 5—a level at which colonization of the stomach by bacteria has been documented—some cyanide is released. These findings vary somewhat from those in our investigations with rat gastrointestinal tracts in that much less amygdalin was hydrolyzed on incubation with the gastric contents of humans than was released on incubation of gastric segments of rats. We postulate that in humans with high gastric acidity, hydrolysis of amygdalin may be delayed until the glycoside leaves the stomach and enters the intestines.

TABLE 1.—*In Vitro Hydrolysis of Amygdalin (CN^- Recovered)*

	CN^- Recovered (nmoles/gram tissue)
Rat gastrointestinal segment	
Stomach	0.049
Duodenum	1.065
Ilium	2.121
Cecum	3.165
Colon	1.112
pH	***nmoles CN^- Released***
Human gastric juice	
2.2-4.1 (5 samples)	0
5.0	34
5.4	35
5.8	53
6.1	0
6.8	64
	nmoles CN^- Released*
Human fecal bacteria	
Escherichia coli	0
Enterobacter aerogenes	43
Streptococcus fecalis	43
Clostridium perfringens	62
Bacteroides fragilis	1,700
Filtrates	0

CN^- = cyanide

*10^9 bacteria

Comments

Discussion of Test Results

It has been known that the harmful effects of amygdalin are directly related to the toxicity of cyanide, which is released following hydrolysis of the parent compound.[1,2,4,5] Our current investigations verify this and show that there is great variability in the effects of amygdalin on rats and that the slope of the LD_{50} curve is not steep. The calculated LD_{50} for rats is somewhere in the range of 15 to 75 times the usual dose of amygdalin recommended for humans by Laetrile advocates. In brief, the oral dose of amygdalin as proposed by its advocates is 500 to 2,500 mg per day. For a 70-kg man, this is 7 to 36 mg per kg of body weight per day, or approximately 1/15 to 1/75 of the LD_{50} dose for rats.

Because humans are seven times more sensitive to the lethal effects of standard chemotherapeutic agents than rats,[6] the difference between the usual dose of amygdalin for man and the theoretical LD_{50} dose for man may vary by a factor of only two to ten. Based upon the rather flat LD_{50} curve, it is reasonable to assume that the toxicity of orally given amygdalin in humans will vary greatly from person to person. This may explain why presumably some have ingested amygdalin and noted no toxic effects, whereas others have become symptomatic and a few have died of cyanide poisoning, one adult dying after ingesting as little as 10.5 grams of amygdalin.[9]

These studies suggest that the status of the bacterial content in the gastrointestinal tract will

have a significant impact on the amount of cyanide released by hydrolysis of amygdalin. Thus, one may postulate that in persons with any gastrointestinal disorder predisposing to proximal colonization of fecal bacteria—such as achlorhydria[19] or spontaneous or surgically induced intraintestinal fistulas—toxicity may be increased following the oral administration of amygdalin. On the other hand, patients on a regimen of orally given antibiotics, especially extended spectrum antibiotics, may have reduced gastrointestinal flora and be less susceptible to amygdalin's toxicity. Results from our studies on the hydrolyzing ability of some human enteric bacteria show that the ability to release cyanide from amygdalin exists in the gastrointestinal tract even in the absence of food stuffs containing the hydrolytic enzymes.

The ability of bacteria to release cyanide from amygdalin has been demonstrated by others. Coop and Blakeley noted cyanide production from amygdalin and from two other cyanogenic glycosides, linamarin and lotaustralin, by the microflora of sheep rumen.[20] In their studies, as in our investigations, hydrolysis was decreased by reducing bacterial numbers, which they accomplish by mechanically washing out the sheep rumen. Human feces have been reported to hydrolyze 45.2 percent of amygdalin as compared with 0.47 percent by mouse feces and 0 percent by monkey feces.[21] In our studies, human stool hydrolyzed 53 percent of amygdalin. The capability of human feces to hydrolyze such a large amount of amygdalin probably explains why a Laetrile enema was nearly fatal to one patient.[14]

Amygdalin administered in conjunction with foods rich in β-glucosidase yields toxic levels of cyanide.[4,5] From our current investigations, we conclude that when amygdalin is given orally or intravenously to rats, even in the absence of food stuffs containing β-glucosidase, appreciable quantities of cyanide are released. In the case of orally given amygdalin, we feel this release of cyanide is due to a great extent to bacterial action in the gastrointestinal tract. In rats fed amygdalin, up to 12.7 percent of the available cyanide in amygdalin was released. Reduction of fecal flora by neomycin reduced the release of cyanide to 1.7 percent.

The Potential for Chronic Poisoning by Cyanide

The pro-Laetrile movement has inappropriately labeled amygdalin as a vitamin (Vitamin B_{17})—a vitamin that is presumably lacking in our diet. They imply that cancer is a nutritional deficiency disease of dietary amygdalin. Using this rationale, the prophylactic administration of amygdalin has been advocated to prevent cancer. Our studies, showing 12.7 percent of available cyanide being released following the oral administration in rats and 53 percent of available cyanide being released following exposure of amygdalin to human feces, suggest that orally given daily doses will expose persons to chronic levels of cyanide. The clinical implication of this becomes staggering when one considers that chronic cyanide poisoning is reported in humans in the tropics and subtropics among natives whose main dietary food is cassava root, which contains linamarin, another cyanogenic glycoside.[22]

Osuntokun and co-workers have shown the association of a degenerative disease in Nigeria, tropical ataxic neuropathy, with chronic cyanide poisoning from the dietary intake of cassava.[23] The most common neurologic damage reported was sensory and motor ataxia, optic atrophy and nerve deafness. Osuntokun states approximately 8.25 mg of cyanide is ingested daily by those who subsist on cassava diets prepared as *gari* meals. The possibility of chronic cyanide poisoning from daily ingestion of Laetrile is overwhelming when one compares this with 30 mg of cyanide ingested with every 500 mg tablet of Laetrile. It is clear that the amount of cyanide contained in the recommended one to five tablets of Laetrile per day is considerably higher than that found in the Nigerian *gari* diets. Some 300,000,000 people eat cassava regularly. Reports of neurologic damage secondary to cyanide are frequent from those countries where these people live. In addition, deaths have been reported following meals of cassava due to cyanide poisoning.

Smith and associates were the first to describe neurologic symptoms consistent with chronic cyanide poisoning in patients ingesting amygdalin.[7] One of their patients was described as having pronounced neuromuscular disorders, including paralysis of both eyelids and lower and upper extremity muscle paresis. The patient had been taking only a single 500 mg amygdalin tablet daily for seven months. When this drug was discontinued, his neurologic symptoms improved dramatically over the subsequent six days. Should some people continue to believe that amygdalin has therapeutic benefits and ingest this cyanogenic glycoside, our studies suggest that signs of chronic cyanide poi-

soning will develop in some. In addition, persons having altered gastrointestinal physiology, such as achlorhydria or spontaneous or surgically induced intestinal fistulas, may sustain acute cyanide toxicity, even death.

The results of our studies have answered the original question we addressed: Is it possible for amygdalin usage to place a person at risk of chronic cyanide exposure? This has been answered in the affirmative, and in so doing a number of additional questions have arisen. These include the following: (1) Why is urinary excretion of amygdalin similar in rats regardless of the route of administration? (2) Why does hydrolysis of amygdalin occur only in the first day of intravenous and oral administration despite the fact that amygdalin's renal clearance continues for five to seven days? (3) Where does conversion of amygdalin to thiocyanate in vivo take place?

While the above questions remain unanswered, we are able to conclude from our studies that Laetrile remains a hazardous drug, lacking not only therapeutic benefit in patients fearing cancer or having cancer, but possessing harmful effects related to cyanide poisoning. We can predict from our studies that if amygdalin is taken chronically, it will produce neurologic damage in humans similar to that seen in persons suffering from tropical ataxic neuropathy, a disorder attributed to chronic cyanide exposure.

REFERENCES

1. Conn EE: Cyanogenic glycosides, *In* Neuberger A, Jukes TH (Eds): International Review of Biochemistry, Biochemistry of Nutrition. Baltimore, Universty Park Press, 1979, pp 21-43
2. Herbert V: Laetrile: The cult of cyanide—Promoting poison for profit. Am J Clin Nutr 32:1121-1158, 1979
3. Griffin GE: World Without Cancer—The Story of Vitamin B_{17}. Thousand Oaks, CA, American Media, 1974
4. Lewis JP: Laetrile (Informed Opinion). West J Med 127: 55-62, 1977
5. Schmidt ES, Newton GW, Saunders SM, et al: Laetrile toxicity studies in dogs. JAMA 239:943-947, 1978
6. Khandekar JD, Edelman H: Studies of amygdalin (laetrile) toxicity in rodents. JAMA 242:169-171, 1979
7. Smith FP, Butler TP, Cohan S, et al: Laetrile toxicity: A report of two cases. Chem Treat Rep 62:169-171, 1978
8. Humbert JR, Tress JH, Braico KT: Fatal cyanide poisoning: Accidental ingestion of amygdalin. JAMA 238:482, 1977
9. Sadoff L, Fuchs K, Hollander J: Rapid deaths associated with laetrile ingestion. JAMA 239:1532, 1978
10. Verdict of the coroner in the matter of the death of Jo Anne Etta Pye, February 1, 1979. Pathologist's Report Jan 26, 1979
11. Investigator's Report December 3, 1978. Alameda County Coroner's Department, County of Alameda, Oakland, CA
12. Anonymous, San Francisco Chronicle, February 6, 1979
13. Anonymous, Medical World News 20:32, 1979
14. Ortega JA, Creek JE: Acute cyanide poisoning following administration of Laetrile enemas. J Pediatr 93:1059, 1978
15. Barrett MD, Hill DC, Alexander JC, et al: Fate of orally dosed linamarin in the rat. Can J Physiol Pharmacol 55:134-136, 1977
16. Rieders F: Cyanides: Type B procedure, *In* CRC Manual of Analytical Toxicology. Cleveland, CRC Press, 1972, pp 120-122
17. Flora KP, Cradock JC, Ames MM: A simple method for the estimation of amygdalin in urine. Res Commun Chem Pathol Pharmacol 20:367-378, 1978
18. Lambert JL, Ramasamy J, Paukstelis JV: Stable reagents for the colorimetric determination of cyanide by modified Konig reactions. Anal Chem 47:916-918, 1975
19. Finegold SM: Intestinal bacteria—The role they play in normal physiology, pathologic physiology, and infection. Calif Med 110:455-459, 1969
20. Coop IE, Blakeley RL: The metabolism and toxicity of cyanides and cyanogenetic glycosides in sheep—I. Activity in the rumen. NZ J Sci Technol, Section A, 30:277-291, 1949
21. Klassen RD, Stavric B: Hydrolysis of amygdalin: Potency of intestinal/fecal flora of various species. Abstracts, 91st Annual Meeting Association of Official Analytical Chemists, 1977, p 18
22. Dorozynski A: Cassava may lead to mental retardation. Nature 272:121, 1978
23. Osuntokun BO: An ataxic neuropathy in Nigeria. Brain 91:215-245, 1968

Refer to: Apfelberg DB, Maldowney B, Laub DR, et al: Breast reconstruction for premalignant and malignant disease—An update. West J Med 134:104-108, Feb 1981

Breast Reconstruction for Premalignant and Malignant Disease—An Update

DAVID B. APFELBERG, MD; BART MALDOWNEY, MD; DONALD R. LAUB, MD; MORTON R. MASER, MD, *and* HARVEY LASH, DDS, MD, *Palo Alto, California*

New concepts in the control of breast cancer and improvements in plastic surgery techniques have facilitated subsequent breast reconstruction. In a six-year period 72 breast reconstructions were carried out in 57 women after surgical treatment for premalignant or malignant breast disease and, in some cases, radiation therapy. The average age of the patients was 48 years and the average interval between the primary cancer operation and breast reconstruction was 42 months. Our experience in these cases has been free of serious complications.

RECONSTRUCTIVE PROCEDURES of female breasts for premalignant or malignant conditions have undergone rapid advances and changes over the last several years. This report updates our reconstructive experience[1] and reviews some modern concepts of breast reconstruction, in particular, new procedures for muscle and skin replacement after full radical mastectomy and nipple/areolar reconstruction.

Developments in breast reconstruction have resulted from three factors. The first is the trend toward less radical surgical procedures, which have been shown to be equally successful in controlling cancer. Second, more women are actively participating in the decisions about surgical procedures and reconstruction. Finally, plastic surgery tissue transfer techniques and silicone mammary implants have improved, allowing greater technical achievements in these procedures.

From the Department of Plastic and Reconstructive Surgery, Comprehensive Center for Breast Disease, Palo Alto Medical Clinic, Palo Alto, California.

Submitted, revised, August 7, 1980.

Reprint requests to: David B. Apfelberg, MD, Palo Alto Medical Clinic, 300 Homer Avenue, Palo Alto, CA 94301.

General Principles of Breast Reconstruction

In 1981 virtually any woman with a mastectomy (even if she has received radiation therapy) can have breast reconstruction. However, most patients with mastectomy eventually adjust emotionally to their condition. Often, the knowledge that a breast can be reconstructed, if desired, can be comforting and supportive to a patient undergoing the stress of breast removal even if the patient chooses subsequently not to have the reconstruction done.

In general, the ideal patient for reconstruction should be free of active (persistent, recurrent or metastatic) disease with a well-healed mastectomy scar, although those patients with evidence of arrested or controlled disease for a substantial time interval can also be considered for the procedure. However, breast reconstruction cannot be done

while other forms of treatment such as x-ray or chemotherapy are under way because of problems of wound healing. The patient should have realistic expectations about the ultimate result of the procedure and understand the possibility of imperfections or deviations from the production of a normal-appearing breast. The fact that multistage procedures may be required, each necessitating a separate anesthesia and hospital admission, must also be recognized. The production of secondary defects and scars resulting from donor areas of flaps and grafts must also be understood.

Plastic surgeons attempt to reconstruct the entire defect (skin, muscle and nipple/areola) but must adapt each reconstruction to the individual patient's needs and desires. A minimal number of procedures with minimal donor defects is also attempted.

Patients and Procedures

Since our original report in 1976[1] of 17 breast reconstructions in ten patients, there has been a total of 72 breast reconstructions carried out in 57 patients (Table 1). The average age of the patient group was 48 years (range 29 to 60), the average interval between the primary cancer operation and the reconstruction was 42 months (range 1 month to 12 years), and the average patient had 1.2 major procedures and hospital admissions and 0.76 minor procedures (usually on an outpatient basis). For example, note in Table 1 that 38 patients with modified or full radical mastectomies had 47 major and 30 minor procedures done. As yet, no patient has died from her primary disease, and there have been no patients with local recurrence or subsequent defined metastatic disease.

Subcutaneous Mastectomy

Subcutaneous mastectomy is a procedure often recommended to those women who are in a high-risk group for the development of breast cancer or who have minimally invasive (in situ) breast carcinoma.[2-4] Although not completely prophylactic in that 100 percent of all breast tissue is not removed[5] (best estimates are from 90 percent to 95 percent), this technique should be considered in the following circumstances: in patients with chronic cystic mastitis necessitating multiple surgical biopsies; in patients with a strong family history of breast cancer in direct lineal relationship,

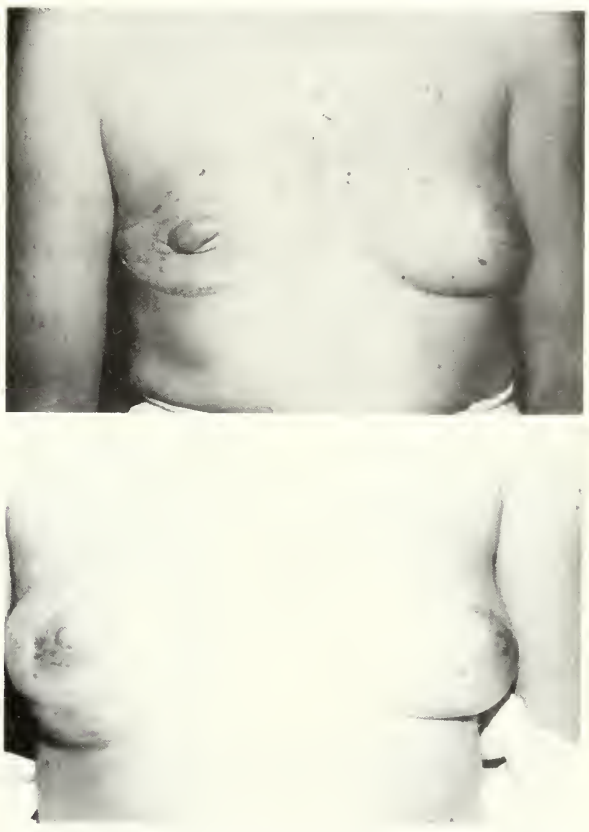


Figure 1.—(Top) Patient following subcutaneous mastectomy of the right breast for carcinoma in situ. **(Bottom)** Contour restoration of the right breast by silicone implant.

TABLE 1.—*Breast Reconstructive Procedures* in 57 Patients for Premalignant and Malignant Disease*

Primary Operation	*No. of Patients*	*Average Age (Years)*	*Average Interval†*	*Major Procedures*	*Minor Procedures*	*Deaths*	*Local Recurrence*	*Metastasis*
Subcutaneous mastectomy	12	43	Immediate—8 patients Delayed—4 patients	12	3	0	0	0
Simple mastectomy	7	43	26 mos	7	3	0	0	0
Modified radical mastectomy ..	21	49 (36-57)	29 mos (7-87)	26	14	0	0	0
Full radical mastectomy	17	50 (36-60)	61 mos (16 mos-12 yrs)	21	16	0	0	0

*Total number of breast reconstructions was 72; some women had both breasts reconstructed. In some women more than one procedure was needed for successful reconstruction.
†Average time interval between primary cancer operation and breast reconstruction.

especially if they have nodular breast tissue; in patients with severe mastodynia plus fibrocystic disease; in patients with ductal or lobular carcinoma in situ,[6] and in some patients with any type of malignant condition in one breast that is known to have a high incidence of bilaterality, especially if fibrocystic disease is present.[7] In 12 patients who had subcutaneous mastectomies, there were eight immediate and four delayed breast reconstructions for the above indications (Figure 1). In three patients subcutaneous mastectomies were done because of chronic inflammation resulting from ruptured silicone breast implants. Statistics of age, interval, number of procedures, complications and subsequent course are reviewed in Table 1.

Simple Mastectomy

Simple mastectomy emerged as one of the early less radical procedures to control breast cancer.[8] Eleven breast reconstructions were carried out in seven patients who had had simple mastectomies of one or both breasts. Indications for this procedure were either severe fibrocystic disease or localized breast cancer (Figure 2). Statistics for this group are reviewed in Table 1.

Modified Radical Mastectomy

The modified radical mastectomy procedure appears now to be the modern alternative to the formerly standard radical mastectomy.[9] The entire breast is removed along with an axillary lymph node resection; however, most often the pectoralis major and minor muscles are spared. Long-term survival as well as lack of local recurrence statistics are equal to those of the more radical procedures. Morbidity is greatly lessened with this procedure and reconstruction can be more easily accomplished by placing the implant beneath the residual muscle. The unsightly hollow beneath the clavicle and the lack of anterior axillary fold are obviated by the modified procedure

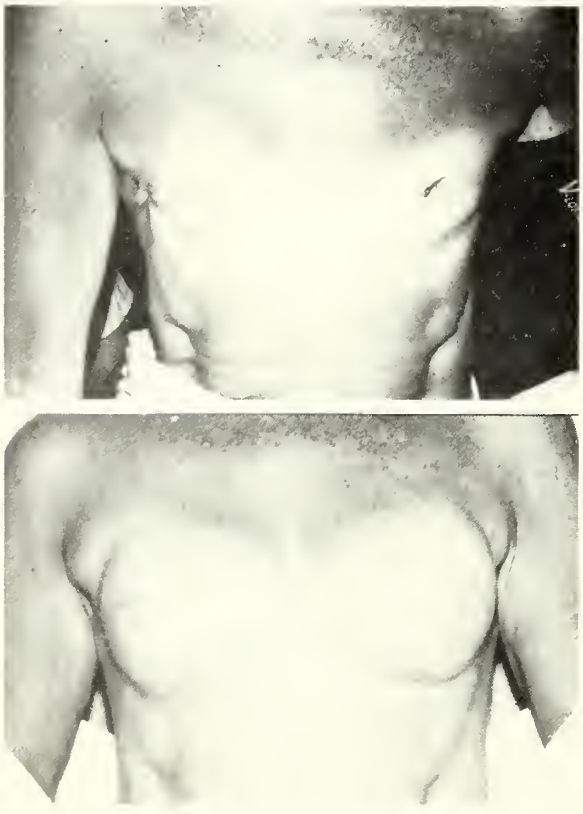


Figure 2.—(Top) Patient following simple mastectomies of both breasts. **(Bottom)** Contour restoration showing size, contour and symmetry of breasts.

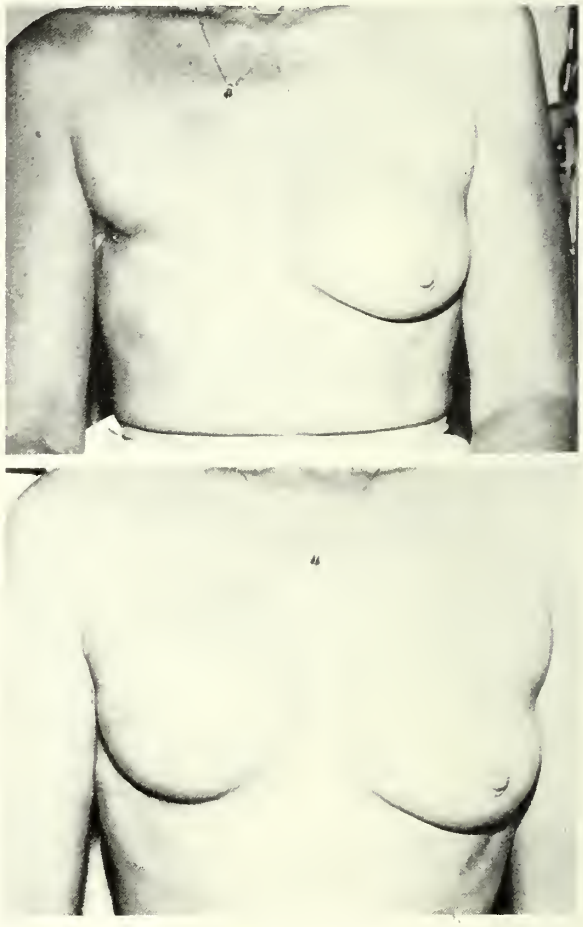


Figure 3.—(Top) Patient following modified radical mastectomy of the right breast. **(Bottom)** Contour restoration of breast mound with good softness and symmetry.

and need not be designed into the reconstructive effort (see Figure 3). Twenty-one breast reconstructions carried out in 21 patients following modified radical mastectomy are reviewed in Table 1.

Radical Mastectomy With or Without Radiation Therapy

Nineteen breast reconstructions were done in 17 patients following full radical mastectomies. Formerly, this condition had been very difficult to correct. However, the advent of the latissimus dorsi myocutaneous flap has revolutionized the reconstructive effort.[10] Based on the thoracodorsal-scapular vascular pedicle, this new flap brings fresh muscle from the back, which can totally restore the lost pectoralis major and minor, and allow restoration of full contour in the chest, axilla and infraclavicular area. In addition, a generous skin island which accompanies the muscle allows very adequate coverage for immediate implant placement (Figure 4A and B). Thus, in one accurate and reliable procedure, full reconstruction of lost skin and muscle can be obtained. The resultant donor defect in the back heals with an inconspicuous scar (which can easily be covered by a standard bra) and no loss of function (Figure 4C and D). Because the donor tissue comes from an area usually spared by radiation therapy, this procedure has allowed reconstruction in five patients with radical or modified radical mastectomy followed by radiation therapy.

Nipple/Areola Reconstruction

Newer techniques of nipple/areolar reconstruction have now produced very satisfactory and relatively symmetrical reconstruction. Older techniques involved labial grafts from the vagina; however, color match and texture were only fair. Similarly, nipple/areola *banking* from the patient's own breast have not proved satisfactory. The best available techniques including (1) sharing of the nipple/areola from the opposite normal breast in the form of equal spirals,[11] (2) split-

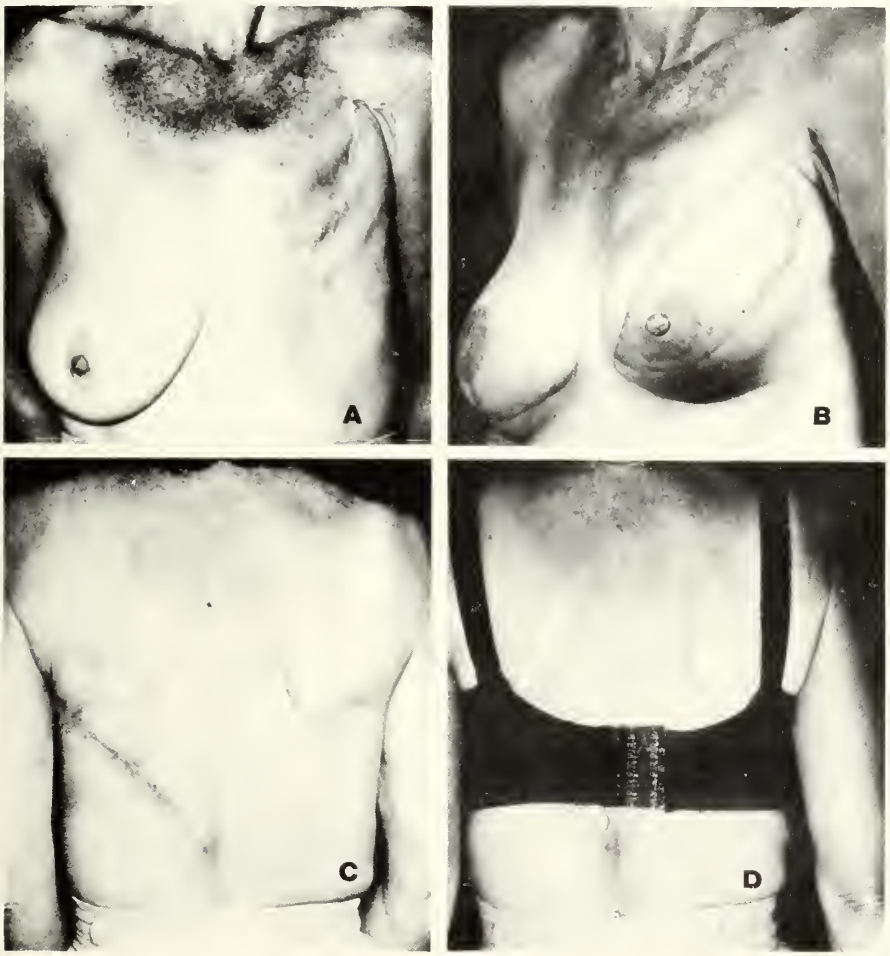


Figure 4.—(A), Status of patient after radical mastectomy and radiation therapy. **(B),** Postoperative reconstruction by latissimus doral flap (note nipple/areola reconstruction). **(C),** Donor defect in back for latissimus flap. **(D),** Coverage of donor defect by a standard bra.

Figure 5.—Nipple/areola reconstruction of left breast using skin and ear grafts.

thickness skin graft from similar pigmented areas of the body (Figure 5), such as the inner thigh or ear[12] and (3) innovative techniques for nipple and Montgomery gland simulation from ear cartilage, as described by Brent and Bostwick.[13] Of course, most patients who undergo reconstruction are more interested in contour restoration than nipple/areolar reconstruction.

Summary

Modern concepts of breast cancer control have resulted in a trend toward less radical procedures which, in turn, have facilitated reconstruction. New procedures such as transfer of the latissimus dorsi myocutaneous flap unit allow easier reconstruction in those cases of full radical mastectomy with or without previous irradiation. Current innovative techniques of nipple/areolar reconstruction afford improved symmetry and appearance. Our experience in breast reconstructions in 57 patients during a six-year period has been free of serious complications.

REFERENCES

1. Apfelberg DB, Maser MR, Lash H, et al: Breast reconstruction for malignant or premalignant disease. West J Med 125:350-353, 1976

2. Goldman LD, Goldwyn RM: Some anatomical considerations of subcutaneous mastectomy. Plast Reconstr Surg 51:501-505, 1973

3. Pennisi VR: Subcutaneous mastectomy and fibrocystic disease of the breast. Clin Plast Surg 3:205-216, 1976

4. Freeman BS: Subcutaneous mastectomy for central tumors of breast with immediate reconstruction. Plast Reconstr Surg 51: 263-267, 1973

5. Pennisi VR, Capozzi A: The incidence of obscure carcinoma in subcutaneous mastectomy. Plast Reconstr Surg 56:9-12, 1975

6. Wheeler JE, Enterline HT, Roseman JM, et al: Lobular carcinoma in situ of the breast. Cancer 34:554-563, 1974

7. Kesseler HJ, Grier WBN, Seidman I, et al: Bilateral primary breast cancer. JAMA 236:278-280, 1976

8. Crile G Jr: Rationale of simple mastectomy without radiation for clinical stage 1 cancer. Surg Gynecol Obstet 120:975-982, 1965

9. Papatestas AE, Lesnick GJ: Treatment of carcinoma of the breast by modified radical mastectomy. Surg Gynecol Obstet 140: 22-26, 1975

10. Bostwick J, Basconez L, Jurkiewicz M: Breast reconstruction after radical mastectomy. Plast Reconstr Surg 61:682, 1978

11. Cronin TD, Upton J, McDonough JM: Reconstruction of the breast after mastectomy. Plast Reconstr Surg 59:1-14, 1977

12. Gruber R: Method to produce better areola and nipples on reconstructed breasts. Plast Reconstr Surg 60:505-513, 1977

13. Brent B, Bostwick J: Nipple-areola reconstruction with auricular tissues. Plast Reconstr Surg 60:353-361, 1977

Refer to: Huebsch LB, Harker LA: Disorders of platelet function—Mechanisms, diagnosis and management (Medical Progress). West J Med 134:109-127, Feb 1981

Disorders of Platelet Function

Mechanisms, Diagnosis and Management

LOTHAR B. HUEBSCH, MD, *and* LAURENCE A. HARKER, MD, *Seattle*

Platelets play an important role in hemostasis, and alterations in platelet function may be the cause of abnormal bleeding in a wide variety of congenital and acquired clinical disorders. Platelet dysfunction may be classified as disorders of (1) substrate connective tissue, (2) adhesion, (3) aggregation and (4) platelet-release reaction. The congenital defects of platelet function, although uncommon, have provided important insights into platelet physiology and pathophysiology and, as a group, are less common, better characterized and more readily classified than the acquired defects.

The severity of bleeding resulting from platelet dysfunction varies greatly and is substantially increased when another defect of hemostasis coexists. A disorder of platelet function is suspected on the basis of the history and physical examination and is confirmed by the finding of a prolonged bleeding time in the presence of an adequate number of platelets. A specific diagnosis often requires measurements of the factor VIII and von Willebrand factor complex and other tests of platelet function. Some of these tests may be available only in specialized laboratories.

Therapy for bleeding episodes resulting from platelet dysfunction is directed at (1) removing or treating the underlying cause of the platelet disorder; (2) replacing the missing plasma cofactors needed to support normal platelet function (such as by the transfusion of cryoprecipitate in patients with von Willebrand disease, and (3) transfusing functional platelets in the form of platelet concentrates in patients with disorders of intrinsic platelet dysfunction.

THE PLATELET REACTIONS of adhesion, aggregation and release are initiated by vascular injury and each has an important role in the mechanisms of hemostasis, arterial thrombus formation, thromboembolism and atherogenesis.[1-4] Disorders of hemostasis may arise from a variety of congenital and acquired abnormalities of platelet function.[5-8] In this review, we discuss clinically significant defects in platelet function, their pathophysiology, diagnosis and management.

From the Department of Medicine (Hematology), University of Washington School of Medicine, Seattle.

Supported by research grants (HL-18645; HL-11775, and HL-07093) from the US Public Health Service and the R. J. Reynolds Industries, Inc.

Reprint requests to: Laurence A. Harker, MD, Department of Medicine, Harborview Medical Center, 325 Ninth Ave., Seattle, WA 98104.

Platelet Physiology

Platelets normally circulate in blood for about ten days as cytoplasmic discs of approximately a

ABBREVIATIONS USED IN TEXT

ADP = adenosine diphosphate
ATP = adenosine triphosphate
β-TG = β-thromboglobulin
cAMP = cyclic adenosine monophosphate
FVIII/VWF = factor VIII/von Willebrand factor
GP = glycoprotein
PG = prostaglandin
PDGF = platelet-derived growth factor
SLE = systemic lupus erythematosus
SPD = storage-pool deficiency
VWD = von Willebrand disease
VWF = von Willebrand factor

10-fl average volume at a concentration of 250,000 ± 50,000 platelets per μl. Under normal circumstances, platelets are nonadherent to all blood elements and to intact vascular endothelium. Vascular disruption exposes blood to subendothelial connective tissue structures of the vessel wall, which initiates the formation of a hemostatic plug.[1,2]

Platelet Structure

Platelets[9] are limited by a typical trilaminar membrane with an outer glycoprotein coat 10 to 20 nm thick that mediates platelet activation reactions (Figure 1). The platelet membrane forms a sponge-like network of tortuous surface connecting channels that expand the surface area of platelets and serves as a conduit for the extrusion of released secretory products. The dense tubular system that is derived from the endoplasmic reticulum interdigitates with the surface connecting system.

The platelet cytoplasm contains three types of granules.[10] Dense α-granules contain storage-pool calcium, serotonin, adenosine triphosphate (ATP) and adenosine diphosphate (ADP). These α-granules contain the following platelet-specific proteins: platelet factor 4 (PF4), β-thromboglobulin (β-TG) and platelet-derived growth factor (PDGF).[11] Coagulation proteins such as fibrinogen, factor VIII, factor V, as well as albumin and fibronectin, are also contained in the α-granules. The lysosomal granules contain hydrolytic enzymes.

Platelets also contain a circumferential band of microtubules that appears to be anchored to the surface membrane and which provides a cytoskeletal structure that maintains the platelet's discoid shape and contractile orientation. The process of platelet activation results in the centripetal movement of these microtubules and the platelet granules. Platelets also contain the contractile proteins actin and myosin, which together

Figure 1.—Platelet ultrastructure. The outer glycoprotein coating mediates platelet reactions. Microtubules (m) form a circumferential cytoskeleton that maintains the platelet discoid. Two types of granules are visible in this electron micrograph, the abundant α-granules (ag) and the less common dense granules (dg). The third type of lysomal granules cannot be differentiated by electron microscopy. The focal collection of smaller glycogen granules (g), microfilaments and tubular systems are also present. (Electron micrograph courtesy of Dr. Russell Ross.)

	1. Surface	2. Adhesion	3. Aggregation	4. Release
Required Factors	collagen microfibrils	surface receptors plasma cofactors e.g., FVIII/vWF	surface receptors plasma cofactors e.g., fibrinogen	surface receptors messengers granules contractile system
Hereditary Defects	Ehlers-Danlos	Bernard-Soulier von Willebrand Disease	thrombasthenia afibrinogenemia	storage-pool deficiency cyclo-oxygenase deficien thromboxane synthetase deficiency
Acquired Defects	scurvy	acquired vWD dipyridamole	fibrin(ogen) degradation products macromolecules penicillins	cardiopulmonary bypass collagen-vascular disease aspirin, etc.

Figure 2.—Platelet hemostatic plug formation. This process includes the sequential events of platelet adhesion to subendothelial structures, platelet aggregation and platelet release reaction. (Electron micrograph courtesy of Dr. Hans Baumgartner.)

constitute about 20 percent of the total platelet protein. Formation of microfilaments reflects the interaction of actin and myosin in the process of platelet spreading, pseudopod formation, secretion of granule constituents and clot retraction.[12] Mitochondria are few in number and structurally simple, and abundant glycogen granules are present in the cytoplasm. Platelets have no DNA, and ribosomes are seen only rarely; a small amount of RNA is present, and protein synthesis has been noted. The cytosol also contains important enzymes involved in platelet metabolism.

Platelet Function[13,14]

Platelet Adhesion

Under normal circumstances, platelets are nonreactive to all blood elements and normal vascular endothelium. A breach in vascular integrity exposes circulating blood to subendothelial structures (Figure 2). The process of platelet adhesion involves the interaction of platelet surface glycoproteins with connective tissue elements of the subendothelium, especially collagen and microfibrils, and requires the von Willebrand* factor (VWF)[1,15] and, possibly, fibronectin as plasma cofactors.

The von Willebrand factor may be synthesized by endothelial cells and circulates in plasma as a multimeric glycoprotein. It is also absorbed onto platelets. When subendothelium is exposed by vessel injury, von Willebrand factor is also absorbed onto exposed collagen.[16] Similarly, fibronectin, a ubiquitous glycoprotein present in platelets, is important in attachment processes of cells. Fibronectin has been postulated to be necessary for the normal interaction of von Willebrand factor with its platelet receptors and with collagen.[17] Platelet adhesion requires a platelet surface

*THE WESTERN JOURNAL's style regarding eponyms is that they are not written in the possessive form; therefore Graves disease, Ewing sarcoma and Paget disease. An explanation may be found on page 78 of the July 1978 issue.

TABLE 1.—*Disorders of Platelet Function*

	Hereditary	*Acquired*
Disorders of substrate connective tissue	Ehlers-Danlos syndrome	Scurvy Amyloidosis
Disorders of adhesion	Bernard-Soulier syndrome von Willebrand disease	Acquired von Willebrand disease Uremia Drugs (eg, dipyridamole)
Disorders of platelet interaction	Thrombasthenia Afibrinogenemia	Fibrin(ogen) degradation products (eg, DIC), liver disease, fibrinolytic liver disease, fibrinolytic therapy Macromolecules (eg, paraproteins and dextran) Drugs (eg, semisynthetic penicillins)
Disorders of release		
Storage granule deficiency		
α-Granule deficiency	Gray platelet syndrome Autosomal recessive disorders	Cardiopulmonary bypass operation
δ-Granule deficiency	Albinism Familial disorders	Immune-mediated release (eg, ITP, collagen vascular diseases) Drugs (eg, reserpine, methysergide, tricyclics, phenothiazines)
Defective release	Cyclooxygenase deficiency Thromboxane synthetase deficiency	Platelet dyspoiesis (eg, leukemia, myeloproliferative syndrome) Drugs (eg, aspirin and other nonsteroidal anti-inflammatory drugs, furosemide, nitrofurantoin) Ethanol Diet
Altered nucleotide metabolism	Glycogen storage disease Fructose-1, 6-diphosphate deficiency	Drugs (eg, phosphodiesterase inhibitors), stimulators of adenyl cyclase (eg, PGI_2, PGE_1)
Others	Platelet factor 3 deficiency	Drugs (eg, heparin, sympathetic blockers, clofibrate, hydroxychloroquine) Diet Viral Infections Hypothyroidism

DIC = disseminated intravascular coagulation; ITP = idiopathic thrombocytopenic purpura; PG = prostaglandin

glycoprotein (GP) complex designated GPIb and GPIs.[18] This complex may act as the platelet receptor for the von Willebrand factor, or, alternatively, the complex may facilitate proper interaction of the von Willebrand factor with its platelet receptor. Absence of this glycoprotein complex causes a serious defect of platelet adhesion.[18,19]

A variety of congenital and acquired abnormalities of platelet function have been attributed to defects in one or more of these factors of platelet adhesion (Table 1).

Platelet Aggregation

Vessel disruption not only induces platelet adhesion but also produces (1) the release of dense-granule ADP from adherent platelets, (2) the formation of small amounts of thrombin and (3) the generation of phospholipase activity to cleave arachidonic acid from membrane phospholipids to synthesize thromboxane A_2.[4,13-15,20,21] These factors—ADP, thrombin and thromboxane A_2—together with exposed collagen may act independently but generally act synergistically to promote the accumulation of additional platelets to the already adherent platelets at the site of vascular damage. Through this process of platelet aggregation the growing platelet mass forms the hemostatic plug (Figure 2).

Platelet aggregation in vitro has been widely used to test platelet to platelet interaction. When platelet agonists such as ADP, epinephrine, collagen or thrombin are added to an opalescent stirred suspension of platelets, the platelets respond by forming aggregates, a process which is recorded as an increase in light transmittance through the platelet suspension. Most platelet agonists induce a biphasic wave of platelet aggregation—primary aggregation, which is the direct result of the agonist-platelet interaction, and secondary aggregation, which is the result of endogenous ADP released during the primary phase of aggregation. Platelet aggregation in vitro is abnormal in a variety of platelet function disorders.

ADP-induced aggregation. Locally formed ADP promotes platelet aggregation by its binding to specific platelet receptors to induce a change in platelet shape from discs to spiny spheres and to decrease adenyl cyclase activity. The interaction of ADP with its surface receptor mobilizes fibrinogen-binding sites on the platelet surface. Fibrinogen binding is essential for platelet-to-platelet interaction.[22] The fibrinogen-binding site contains the glycoprotein complex designated GPIIb and GPIIIa.[18,19] The GPIIIa component of this complex may also serve as the surface membrane anchor for the contractile protein actin, thereby providing a direct link between the membrane structures involved in aggregation and the contractile-secretory apparatus of platelets. Lack of fibrinogen or absence of the putative fibrinogen receptor GPIIb and GPIIIa substantially impairs platelet aggregation.

Epinephrine-induced aggregation. Epinephrine induces platelet aggregation. Primary interaction of epinephrine with its platelet α-receptor induces reversible aggregate formation and inhibition of adenyl cyclase activity. Second-wave aggregation is mediated through the release of ADP from the δ-granules and through the synthesis of thromboxane A_2. Although the concentration of catecholamines usually found in the circulation may not be sufficient to cause aggregation, they may, however, sensitize the platelets to the effects of other aggregatory factors. The secondary phase of aggregation induced by epinephrine is blocked by inhibition of cyclo-oxygenase as well as by deficiency of δ-granule ADP.

Collagen-induced platelet aggregation. In vitro, collagen induces primary platelet aggregation.[23] Low concentrations of collagen cause a few platelets to adhere to the collagen, and these adherent platelets then release ADP and thromboxane A_2. In vitro, this response to small concentrations of collagen is partially inhibited by inactivation of platelet cyclo-oxygenase or by the removal of released ADP. However, in vivo the collagen platelet interaction provides a strong stimulus for the release of granule contents. Adherent platelets undergo the release reaction even in the presence of drugs (such as aspirin) that inhibit platelet cyclo-oxygenase.

Thrombin-induced aggregation. Thrombin plays a central role in the growth and stability of the platelet hemostatic plug.[24,25] Vessel injury leads to rapid local production of thrombin in small amounts, which then interacts with platelet receptors. Receptor stimulation may lead to platelet aggregation directly. Thrombin also stimulates thromboxane A_2 synthesis and causes the release of platelet δ-granule ADP. Thus, thrombin magnifies its effect on platelet aggregation and release by activating several additional pathways. Thrombin also causes the appearance of receptors for factors

Va and Xa, which enhances the conversion of prothrombin to thrombin on the platelet surface, in turn allowing for fibrinogen to be converted to fibrin.[24] Polymerized fibrin adheres to the surface of platelets and imparts stability to the platelet aggregate. Fibrin may be formed from platelet fibrinogen independent of plasma fibrinogen.

Platelet Release Reaction

The release reaction is the secretory process whereby substances stored in platelet granules are extruded from the platelet.[10] ADP, epinephrine, collagen and thrombin are the physiologically important agents that induce such release. The α-granule contents are the most readily released; δ-granule release requires a somewhat greater platelet stimulus, and lysosomal granule contents are released only with potent stimuli such as concentrated collagen or thrombin.[10]

The exact biochemical reactions induced by ADP, collagen and thrombin that lead to granular release remain unclear. However, the release reaction, like platelet adhesion and aggregation, is a membrane-mediated process involving specific glycoprotein receptors located on the platelet surface. Receptors are present for ADP, epinephrine, collagen and thrombin, the physiologically important agents that induce platelet release. The binding of these agonists initiates the formation of intermediaries that relay the signal to the contractile-secretory apparatus.[25] The system of independent but interactive second messengers is thought to trigger a transfer of free, ionized calcium as the final mediator in the formation of actomyosin microfilaments, which then execute the release reaction.[26]

The platelet arachidonic acid pathway illustrates this sequence. It has been worked out in some detail,[27,28] whereas the intermediate pathways specific for collagen, ADP and thrombin remain to be characterized. Arachidonic acid is stored in platelet phospholipids, especially monophosphotidylinositol. Arachidonic acid is cleaved from these phospholipids either by phospholipase C and diacylglycerol lipase or by phospholipase A_2.[29] Free arachidonic acid is subsequently converted to the prostaglandin endoperoxides PGG_2 and PGH_2 by platelet cyclo-oxygenase. The unstable endoperoxides are converted to thromboxane A_2, a labile but potent substance capable of inducing platelet aggregation and release, which is also a potent arterial vasoconstrictor. The short-lived thromboxane A_2 spontaneously breaks down to thromboxane B_2, a stable inactive metabolite measurable by radioimmunoassay. ADP, thrombin and collagen can all induce platelet aggregation and the platelet release reaction directly, but usually these agents also activate the platelet arachidonic acid pathway. It is not clear how membrane stimulation by collagen, thrombin or ADP initiates thromboxane A_2 synthesis. However, these agents may, in part, act by their ability to raise free, ionized, intracellular calcium levels, which in turn activates calcium-sensitive phospholipases.

Thromboxane A_2 synthesis is inhibited by aspirin and other nonsteroidal anti-inflammatory drugs that act by inhibiting platelet cyclo-oxygenase.[30] The fact that aspirin can induce a complete block of this pathway, and in so doing only induces a mild defect in hemostasis, suggests that the important physiological agents that induce platelet release and aggregation can act on platelets independent of activation of the arachidonic acid pathway. This suggests that activation of the platelet arachidonic acid pathway acts only as a mechanism of potentiation or amplification of physiological stimuli leading to aggregation and release but is not critical to platelet function.

Agents that inhibit the platelet release reaction generally increase adenyl cyclase activity and elevate platelet cAMP (cyclic adenosine monophosphate) levels, causing free calcium levels to drop and, thereby, inhibiting the interaction of actin and myosin. Inhibitory effects exerted on platelets by such prostaglandins as PGD_2, PGI_2 and PGE_1 are initiated by the binding of these platelet antagonists to specific surface membrane receptors.[31]

A wide spectrum of acquired and congenital abnormalities of the platelet release reaction have been identified and, on the whole, result in mild bleeding disorders (Table 1).

Disorders of Platelet Function

Disorders of Substrate Connective Tissue

Ehlers-Danlos Syndrome

Some inherited disorders of collagen biosynthesis such as the Ehlers-Danlos syndrome are characterized in part by extremely fragile skin and easy bruising. Such patients may sustain extensive ecchymoses from minimal trauma. In Ehlers-

Danlos syndrome type IV, there is a pronounced propensity for easy bruising and a predisposition to sudden death from spontaneous hemorrhage as a result of arterial rupture. Abnormal bleeding is thought to be the result of defective connective tissues (Table 1). For example, Ehlers-Danlos syndrome type IV is characterized by a deficiency of type III collagen in the skin and vessel wall.[32] Poor connective tissue support leads to a propensity for vessel wall disruption, poor vessel wall retraction after disruption and extension of the hematoma along fragile tissue planes. Intrinsic platelet function is usually normal in this syndrome, but impaired platelet adhesion to the disrupted defective vessel wall impairs platelet plug formation and leads to a bleeding disorder simulating qualitative platelet defects. The diagnosis is suspected on clinical grounds together with normal findings on in vitro tests of hemostasis. Confirmation requires documentation of the abnormal collagen in the subcutaneous tissue. There is no known specific therapy for the bleeding tendency in these patients.

Scurvy

Scurvy, an acquired disorder now rarely seen, may be associated with a significant bleeding tendency, the result of a connective tissue defect caused by vitamin C deficiency.[33,34] The deficiency impairs the synthesis of hydroxyproline, an important building block of normal collagen. The resultant defective collagen weakens the connective tissue, producing hemorrhagic manifestations such as gingival bleeding, and subcutaneous and muscle hemorrhages. Finding perifollicular petechiae on physical examination is characteristic. The bleeding time is slightly prolonged and in vitro platelet function is normal. The disorder responds within one to three weeks following oral administration of vitamin C.

Amyloidosis

Purpura may be acquired from the diffuse vascular and mucosal infiltration that occurs in systemic amyloidosis.[35,36] Periorbital purpura is typical. The risk of hemorrhage is high after minor surgical procedures such as skin, gingival or liver biopsy. When amyloidosis occurs in association with plasma cell myeloma, hemostatic defects resulting from the latter condition may further aggravate the bleeding tendency. In a few patients with amyloidosis, an acquired factor X deficiency has also developed.[37] In vitro platelet function is normal. Management of such patients includes the avoidance of liver biopsy because this procedure may lead to serious bleeding after biopsy. Primary treatment is directed at the underlying disorder.

Disorders of Platelet Adhesion

Bernard-Soulier Syndrome

The Bernard-Soulier syndrome is a rare, familial bleeding disorder of moderate severity characterized clinically by epistaxis, menorrhagia, and cutaneous and visceral hemorrhages.[7] The platelet count is variable, and on blood film the platelets appear enlarged because of their flat disc shape. The bleeding time is substantially prolonged—that is, more than 20 minutes. Ristocetin-induced platelet aggregation is absent and is not correctible by the addition of exogenous von Willebrand factor.[6,13] Platelet aggregation to such other aggregating agents as ADP, collagen, epinephrine and thrombin is normal.

The impairment of hemostasis in this syndrome is secondary to an intrinsic defect of platelet adhesion to subendothelium.[38] The membrane glycoprotein of platelets from these patients shows a deficiency of membrane glycoproteins designated GPIb and GPIs (glycocalicin). There is evidence to support the hypothesis that the absence of these membrane glycoproteins is responsible for the observed functional defect. It has been postulated that this glycoprotein I complex may normally act as the platelet receptor through which the von Willebrand factor mediates not only the platelet subendothelium interaction but also the in vitro ristocetin-induced aggregation of platelets.[18]

The diagnosis is based on the patient's history and on the presence of the morphological, functional and biochemical characteristics outlined above. Therapy is limited to the transfusion of platelet concentrates for control of threatening hemorrhage. The condition appears to improve with age, but fatal bleeding episodes have been reported.

Von Willebrand Disease

Von Willebrand disease (VWD) is a relatively common heterogeneous group of congenital bleeding disorders,[39-42] in which a prolonged bleeding time and impaired hemostasis are the result of

TABLE 2.—*Nomenclature of Factor VIII/von Willebrand Factor Used in This Review**

Factor VIII procoagulant activity (FVIII:Co). Clot-promoting activity that is absent in severe hemophilia A, but normal or decreased in vWD.
Ristocetin cofactor (FVIII:RCo). Activity that supports ristocetin-induced platelet aggregation; it is normal in hemophilia A, but reduced or absent in most (but not all) cases of vWD.
Factor VIII-related antigen (FVIII:Ag). Antigen of FVIII/vWF, detected by heterologous antibodies. It is normal in hemophilia A, but may be normal, decreased or absent in vWD.
Factor VIII/von Willebrand factor (FVIII/vWF). Complex of FVIII:Co, FVIII:Ag and FVIII:RCo. It is present in normal plasma as high multimers.

vWD = von Willebrand disease

*Source: Zimmerman et al.[44]

quantitative and qualitative abnormalities of the factor VIII/von Willebrand factor (FVIII/VWF) (Table 2).

The classic form of von Willebrand disease is inherited as an autosomal dominant trait and is characterized clinically by a mild to moderate bleeding tendency that frequently involves epistaxis, gingival bleeding, menorrhagia or postoperative bleeding. Gastrointestinal, muscle and joint bleeding are much less common. The template bleeding time is prolonged. Biochemically, two main variants can be defined on the basis of laboratory findings. In type 1 there is a concordant decrease in FVIII:Co, FVIII:Ag and FVIII:RCo (Table 2). In type 2, a qualitative abnormality of FVIII/VWF complex can be shown on radiocrossed immunoelectrophoresis, which shows the absence of the larger molecular forms of the FVIII/VWF complex.[43]

A less common but more severe form of von Willebrand disease is transmitted as an autosomal recessive trait and is clinically similar to hemophilia. Muscle, gastrointestinal and joint bleeding, as well as mucosal bleeding are the most common clinical manifestations. The disease is inherited from both parents, although the heterozygote parents are usually clinically normal or have only a mild bleeding tendency with modest abnormalities of the FVIII/VWF complex. The template bleeding time in affected patients is greatly prolonged. Both qualitative and quantitative abnormalities of the FVIII/VWF can be observed on crossed immunoelectrophoresis. Such studies have shown that the FVIII:Ag level is severely depressed and that the very small amount of antigen that is present is structurally abno mal.[44]

The quantitative and qualitative abnormalities of FVIII/VWF impair hemostasis by virtue of the defect of platelet adhesion that results from decreased platelet interaction with subendothelium, a process that is normally supported by high molecular weight multimers of FVIII/VWF. This abnormality is best observed by failure of platelets to adhere to segments of de-endothelialized artery in patients with VWD.[45] This defect of adhesion to subendothelium is most pronounced at sites of high-shear flow as found in the microcirculation. The defect of adhesion is corrected by the addition of normal plasma that contains FVIII/VWF, such as is present in cryoprecipitate.[46] The second factor that contributes to bleeding in some patients appears to be the FVIII:Co that is seen in the autosomol recessive variety of von Willebrand disease. In some such cases the FVIII procoagulant activity may be depressed to the same degree as in hemophilia, and this may be an important additional mechanism for abnormal hemostasis in this disease.

The diagnosis in von Willebrand disease is usually based on the finding of a combination of an inherited bleeding disorder characterized by a prolonged bleeding time and a combination of biochemical abnormalities of FVIII/VWF—typically, concordantly low FVIII:Co, low FVIII:Ag and decreased or absent ristocetin-induced platelet aggregation.[39,47] However, it is becoming increasingly apparent that von Willebrand disease represents a heterogeneous group of diseases both clinically and biochemically. While no single test is diagnostic, the measurement of FVIII:RCo has been found to be the most consistent biochemical abnormality. Even this test may give false-negative results as shown in a recent report of a subgroup of autosomal dominant VWD with accelerated ristocetin-induced platelet aggregation.[48]

The preferred treatment for bleeding problems in patients with von Willebrand disease is administration of cryoprecipitate and, occasionally, concomitant epsilon aminocaproic acid. The aim of therapy with cryoprecipate is to achieve hemostatic levels of FVIII procoagulant activity rather than the normalization of the bleeding time, which is achieved only transiently. Using the principles of transfusion therapy developed for hemophilia A, surgical procedures can be safely carried out in these patients, and most bleeding episodes can be well controlled.[47,49]

Acquired von Willebrand disease.[50-53] An in-

creasing number of patients are being described who have a von Willebrand-like defect as an acquired phenomenon secondary to the development of an autoimmune disease (such as systemic lupus erythematosus [SLE]) or a lymphoproliferative syndrome (such as lymphoma or multiple myeloma). The resultant acquired bleeding disorder has been termed von Willebrand syndrome. Patients may present with a bleeding diathesis similar to that seen in the inherited types of von Willebrand disease. The molecular defect is the absence of adequate amounts of functionally active VWF, which leads to a defect in platelet adhesion. In several patients this has been due to an antibody directed against the von Willebrand factor, with either rapid clearance of this complex or interference with its normal function. In other patients, such as those with lymphoproliferative disorders, the malignant cells may avidly absorb active VWF, leaving the patients depleted of this factor. The end result is a defect in platelet adhesion detectable by a prolonged bleeding time and, in some patients, a clinically significant bleeding disorder. This bleeding tendency may remit if the primary disease is successfully treated.

Uremia

Uremia produces an extrinsic platelet defect as a result of the progressive accumulation of metabolic products in the blood.[54] In untreated patients with uremia the template bleeding time is usually greater than 30 minutes and, predictably, shortens to near normal in patients treated with peritoneal dialysis.[55] Hemodialysis is less effective in this regard.

The mechanism of the platelet defect in uremia remains unclear, but appears to be due in part to the accumulation of uncleared metabolites such as guanidinosuccinic acid, phenol and phenolic acids.[56] These metabolic end products can inhibit platelet procoagulant availability and aggregation of platelets to ADP, collagen and epinephrine in vitro.

Therapy for the platelet disorder is adequate dialysis, which will tend to restore the prolonged bleeding time towards normal. Occasionally, platelet concentrates are necessary for control of bleeding during surgical procedures.

Drugs

Dipyridamole is an antiplatelet agent used in the prevention of arterial and venous thrombosis. Dipyridamole diminishes platelet adherence to collagen, the subendothelium and artificial surfaces in vivo.[57-60] Increased platelet consumption in humans is normalized by the administration of dipyridamole, a phosphodiesterase inhibitor that increases platelet cAMP levels and possibly potentiates the antiaggregatory activity of endogenous prostacyclin.[61] Despite these antithrombotic actions, the administration of dipyridamole does not prolong bleeding time and has no detectable influence on hemostatic function in vivo at the doses usually given. Dipyridamole has been shown to decrease the thromboembolic complications of prosthetic heart valves,[62] and aspirin potentiates the antithrombotic effects of the drug. In a recent major trial using dipyridamole and aspirin, a reduced incidence of coronary disease (coronary deaths and nonfatal infarction) was reported.[63]

Under physiological conditions of flow and hematocrit, drugs such as sulfinpyrazone and aspirin, both of which inhibit cyclo-oxygenase, do not inhibit the adherence of the initial layer of platelets to the subendothelium or prevent the adherent platelets from releasing their constituents. These drugs do, however, inhibit subsequent platelet aggregation, probably by preventing thromboxane A_2 formation. Sulfinpyrazone, in contrast to aspirin, does not prolong the bleeding time and does not impair hemostatic function when given in pharmacological doses.[57]

Disorders of Platelet Interaction

Thrombasthenia

Thrombasthenia is a rare congenital bleeding disorder transmitted as an autosomal recessive trait.[64,65] The bleeding tendency starts early in life, is of variable severity and is characterized by cutaneous, mucosal and postoperative bleeding. The prolonged bleeding time in the presence of a normal platelet count seen in this disorder is due to an abnormality of platelet aggregation, which is manifested as an absence of in vitro platelet aggregation following the addition of ADP, epinephrine, collagen or thrombin.

The defect in thrombasthenia is an abnormality of platelet to platelet interaction which results in an inability to form a hemostatically effective cohesive platelet aggregate. Platelet adherence to subendothelial connective tissue structures is normal. Although thrombasthenic platelets fail to aggregate in vitro to the usual aggregating agents, these same agents do produce normal changes in platelet shape and a near normal release reaction.

This defect in platelet to platelet interaction is associated with an inability of the thrombasthenic platelets to bind fibrinogen to their surface following ADP activation.[22] This failure of fibrinogen binding in thrombasthenia may be related to a deficiency in the platelet surface glycoproteins designated GPIIb and GPIIIa.[18,19] It has not been actually shown that this glycoprotein complex is the fibrinogen receptor. Alternatively, it has also been postulated that the glycoprotein IIb and IIIa complex serves as the membrane anchor for the actin component of the cytoskeleton. A deficiency of this glycoprotein complex may then lead to a failure in the contractile process involved in platelet orientation during the formation of a cohesive platelet aggregate.

The recent development of a monoclonal antibody to the GPIIb and GPIIIa complex may clarify not only the nature of the defect in thrombasthenia, but may also provide greater insight into normal platelet aggregation.[66] In addition, the use of such an antibody has allowed detection of the heterozygote state of this condition by measuring the moderate decrease in the amount of GPIIb and GPIIIa on the platelet surface.

The diagnosis is made on the basis of the history, prolonged bleeding time and platelet aggregation abnormalities described above. The transfusion of platelet concentrates for bleeding episodes is effective therapy for this condition. Even with this mode of treatment, however, the development of antibodies to glycoproteins of normal platelets in some patients may make platelet concentrates only transiently beneficial.

Afibrinogenemia

The bleeding time is prolonged in this rare autosomal recessive condition, probably because there is insufficient binding of fibrinogen to platelet surfaces for significant platelet to platelet interaction.[67] ADP-induced platelet aggregation is reduced, a defect that can be corrected in vitro by the addition of fibrinogen. This condition demonstrates the crucial mediating role played by fibrinogen in platelet aggregation. Bleeding episodes are treated with the transfusion of fibrinogen as cryoprecipitate.

Proteolytic Products of Fibrin(ogen)

Proteolytic degradation products of fibrin and fibrinogen may inhibit platelet plug formation.[68] These complexes are increased in a number of clinical conditions, such as disseminated intravascular coagulation, fibrinolytic therapy with urokinase or streptokinase, and liver disease. Platelet function may be impaired by fragments X, Y and D, all products of plasmin digestion of fibrin(ogen). These products bind to fibrin monomers and interfere with fibrin polymerization and platelet-fibrin interaction.[69]

The relative importance of platelet dysfunction in some of these clinical situations is not entirely clear because other aspects of hemostasis are often profoundly impaired. For example, patients with liver disease may also have a deficiency of vitamin-K-dependent coagulation proteins, increased fibrinolytic activity, and quantitative and qualitative platelet defects.[70]

Treatment is directed at the underlying disease process. Administration of platelet concentrates may be of significant benefit in those patients with combined qualitative and quantitative platelet defects.

Dysproteinemia

The monoclonal immunoglobulins in the dysproteinemia syndromes, such as multiple myeloma, sometimes induce a disorder of platelet function.[71] In such patients the bleeding time is prolonged. Platelet adhesion and aggregation are impaired and platelet procoagulant activity is also reduced. The platelet defect is thought to be the result of interference by immunoglobulins, especially IgA, of platelet receptor-mediated reactions, presumably as a result of coating of the platelet surface by the paraprotein.

Like other acquired defects of platelet function, the hemostatic defect in these disorders is complex, with the frequent coexistence of thrombocytopenia, impaired fibrin formation, and hyperviscosity as possible additional contributing factors. The severity of the bleeding disorder correlates with the prolongation in bleeding time and the level of paraprotein. An improvement is usually seen when therapy of the underlying plasma cell dyscrasia successfully lowers the protein level. However, with high levels of monoclonal protein, therapy with platelet concentrates may be ineffective. Plasmaphoresis may lower the paraprotein level suddenly and ameliorate the bleeding tendency in some patients.

Dextran

Dextran, a high molecular weight polysaccharide derived from sucrose, has been used in the

prophylaxis of postoperative deep venous thrombosis and pulmonary thromboembolism.[72] Therapeutic doses of dextran prolong the bleeding time and decrease platelet aggregation and procoagulant activity.[73] The exact mechanisms of platelet dysfunction remain uncertain, although coating of the platelet surface has been assumed. Bleeding as a complication of administration of dextran requires its discontinuation and, occasionally, platelet transfusions.

Drugs

A number of antibiotic drugs have significant effects on platelet function. These effects are of particular importance in patients receiving intensive chemotherapy. Carbenicillin is often used in pancytopenic patients for suspected sepsis in doses that cause significant platelet dysfunction.[74] Ticarcillin, penicillin G, ampicillin and cephalosporins, although less well studied than carbenicillin, appear to induce a similar defect when given in high enough doses.

Carbenicillin prolongs the bleeding time as a result of a defect in platelet to platelet interaction. Decreased sensitivity to the aggregating effects of ADP, with absent primary and secondary aggregation has been seen. The mechanism is unclear, but it has been postulated that the antibiotic drug or its metabolites inhibit interaction of platelet agonists (such as ADP and epinephrine) with von Willebrand factor and their respective platelet surface glycoprotein receptors.[75]

Patients with severe thrombocytopenia who are receiving carbenicillin treatment may have a bleeding tendency at an absolute platelet level that is considerably higher than might be expected in patients not receiving these antibiotic drugs.[76] The use of platelet concentrates in such patients is then recommended at a higher platelet count than the 5,000 platelets per μl generally recommended for those patients who do not have a qualitative defect in addition to severe thrombocytopenia.[76] It is unclear whether ticarcillin may be effectively substituted for carbenicillin at doses that do not affect platelets to the same degree.

Disorders of Platelet Release Reaction

Abnormalities of platelet release can be divided into deficiencies of one or more of the platelet granules, disorders of thromboxane A_2 synthesis from membrane arachidonic acid, or conditions in which altered cAMP metabolism changes the reactivity to platelet agonists.

Granule Storage-Pool Deficiency

α-Granule depletion. A small number of patients have an inheritable deficiency of platelet α-granules (α-SPD), a condition termed the gray platelet syndrome.[77] The platelets appear enlarged and gray on a Wright-stained blood film. The platelet function defect, which is characterized by a deficiency of α-granules and their contents, including PF4, β-TG, PDGF, platelet fibrinogen and fibronectin.[78] These platelets have normal dense granules and lysosomal granules. Clinically, these patients present with a syndrome of easy bruisability. The bleeding time and platelet aggregation induced by ADP, thrombin, and collagen are minimally abnormal. Mild to moderate thrombocytopenia is also present in some, and may improve with splenectomy. The fact that an α-granule deficiency induces only a mild disorder of platelet function is consistent with the notion that α-granules play a minor role in normal hemostasis.

An acquired α-granule depletion has been observed in patients during open-heart and pump-oxygenator bypass operations.[79] These patients are at risk for serious bleeding as a result of the procedures and the accompanying acquired defects in hemostasis. There are a number of potential contributing factors in the hemostatic defect during cardiopulmonary bypass operations, including a reduction in the levels of coagulation factors, heparinization or its inadequate reversal, increased fibrinolytic activity and thrombocytopenia; however, the most important is a transient defect in platelet function.[80] With the onset of the cardiopulmonary bypass operation, the bleeding time becomes greatly prolonged, in parallel with platelet α-granule release as indicated by substantial elevations in plasma PF4 and β-TG. At the end of a bypass operation, the remaining circulating platelets are partially depleted of their α-granules. This deficiency persists despite the bleeding time returning to normal within one to two hours after completion of bypass oxygenation. The dense granules do not undergo release in this setting. However, in some patients the bleeding time after a bypass operation remains prolonged and may be the cause of excessive postoperative bleeding. Bleeding from a persistent platelet function defect after a bypass operation

should be treated by administering platelet concentrates even when the platelet count is adequate.

δ-Granule deficiency. Congenital dense-granule storage-pool deficiency (δ-SPD)[81,82] is a term used to designate a group of lifelong platelet function disorders clinically manifested by easy bruisability, menorrhagia and excessive postoperative bleeding. In some patients oculocutaneous albinism is also present, in which case the disorder is referred to as the Hermansky-Pudlak syndrome. The bleeding time is moderately prolonged and in vitro platelet aggregation to collagen is impaired as is the second phase of aggregation to ADP and epinephrine. The platelet count is normal or slightly decreased, and platelet morphology under light microscopy is normal. Electron microscopy shows a deficiency of δ-granules and, usually, a normal number of α-granules. Biochemically, platelet ATP and ADP are below normal and the ATP to ADP ratio is increased (because more ADP than ATP is contained in the δ-granules). The congenital δ-granule deficiencies can be distinguished from the aspirin-like platelet defects by the normal ATP to ADP ratio and the normal number of δ-granules seen on electron microscopy in the latter syndromes.

The dense-granule deficiencies are not a homogeneous group of disorders and can be separated into several subgroups on the basis of associated biochemical abnormalities.[82] Some patients may have an associated partial or complete deficiency of α-granules. Management involves avoidance of aspirin therapy as well as judicious use of platelet concentrates for bleeding episodes when clinically indicated. On the whole, these disorders are benign, although occasionally easy bruising can be troublesome.

Chronic immune thrombocytopenic purpura,[83] autoimmune hemolytic anemia,[84] and systemic lupus erythematosus (SLE)[85] occasionally have been associated with an acquired platelet defect characterized by a prolonged bleeding time and decreased aggregation to collagen, thrombin and ADP. In such circumstances, an acquired deficiency of dense granules and dense granular contents is seen. Antiplatelet antibodies or antigen-antibody complexes associated with these underlying diseases may act on circulating platelets by inducing the release reaction and causing the depletion of dense-granule ADP and serotonin.[86] It appears then that human antiplatelet antibodies are capable of inducing a wide spectrum of platelet defects, ranging from profound thrombocytopenia to subtle qualitative defects of platelet function. Specific mechanisms whereby the platelets in such conditions become depleted of dense-granule contents are not known, although activation of the complement system appears to be associated in some instances. The diagnosis should be suspected in a patient who has an inappropriately long bleeding time or bleeding for the degree of thrombocytopenia in a setting of any of the immune-mediated diseases mentioned above. Therapy is generally directed at the underlying condition.

In both congenital and acquired dense-granule depletion, it appears that the deficiency of ADP underlies the bleeding tendency seen in these patients. Serotonin, on the other hand, although also low in such conditions, appears to have no well-established role in human platelet function. Selective depletion of platelet serotonin by such drugs as reserpine and the phenothiazines causes no detectable disorder of platelet function in vivo.

Abnormalities of Platelet Release Reaction

A heterogeneous group of mild bleeding disorders involving defective platelet release mechanisms has been observed. These disorders are characterized by mild to moderate prolongation of the bleeding time with impaired in vitro platelet aggregation induced by ADP, collagen and epinephrine, but with normal platelet δ- and α-granule content.

A group of patients have been described with (1) a history of intermittent excessive bleeding in response to trauma, in association with a normal platelet count and a normal or minimally prolonged bleeding time, (2) an exaggerated prolongation of the bleeding time in response to aspirin therapy and (3) abnormal platelet aggregation suggestive of a defect in the platelet release mechanism. This has been termed the "intermediate syndrome" of platelet dysfunction.[87] The underlying defect is not known.

Recently, in some of these patients a specific platelet defect has been identified.

Cyclo-oxygenase deficiency. In a number of patients a deficiency in platelet cyclo-oxygenase has been confirmed.[88] This condition is characterized by defective platelet aggregation to collagen as well as absent second-phase aggregation to ADP and epinephrine. The platelets fail to aggregate to arachidonic acid, but do aggregate with

addition of the endoperoxides, such as PGH_2.[89] The patients have a normal ATP to ADP ratio and their platelets appear normal by microscopy. Clinically, these patients have a mild impairment of hemostasis with easy bruisability, menorrhagia and excessive postoperative bleeding. The impairment is the result of an inability of platelets to generate thromboxane A_2, a potent inducer of the platelet release reaction and of platelet aggregation. Platelet adhesion is normal. From a diagnostic point of view, it may be difficult to exclude aspirin ingestion as the basis for the observed abnormalities. It is imperative that a patient not take aspirin for two weeks before doing any platelet function tests for this and other disorders.

Thromboxane synthetase deficiency. Several patients with a bleeding disorder of moderate severity due to presumed thromboxane synthetase deficiency have been described.[90,91] The bleeding time is prolonged and in vitro platelet aggregation to ADP, collagen and epinephrine is impaired. Furthermore, platelets in this disorder fail to aggregate to arachidonic acid or the endoperoxide PGH_2. Failure to aggregate in response to the endoperoxides distinguishes this syndrome from platelet cyclo-oxygenase deficiency, where PGH_2-induced aggregation is normal. In one case of congenital thromboxane synthetase deficiency, the patient's bleeding responded to platelet transfusion.

Diet. Thromboxane A_2 is generated from membrane arachidonic acid. Diets rich in another fatty acid, eicosapentaenoic acid, as consumed by Eskimos, for example, leads to replacement of phospholipid arachidonate by phospholipids rich in eicosapentaenoic acid. This latter fatty acid is a poor substrate and in effect leads to decreased thromboxane A_2 synthesis and a slight prolongation of the bleeding time. It has been postulated that such dietary manipulations, by impairing platelet function and possibly enhancing synthesis of antiaggregatory prostaglandins by the vessel wall, may retard the development of arterial thrombosis and atherosclerosis.[92,93]

Platelet dysfunction due to abnormalities of hematopoiesis. Acute nonlymphocytic and acute lymphocytic leukemia as well as the preleukemic states that sometimes precede them, are often associated with quantitative as well as qualitative abnormalities of platelet function.[94,95] The functional defects are variable and often complex, but include (1) giant platelets, (2) abnormal cytoplasmic granules, (3) defective granule migration, (4) deficient storage-pool content and (5) impaired thromboxane A_2 synthesis. It is important to recognize this qualitative defect as it may be superimposed on the thrombocytopenia in these disorders.[96]

The myeloproliferative syndromes—polycythemia vera, agnogenic myeloid metaplasia and idiopathic thrombocythemia—as well as chronic myelogenous leukemia are clonal disorders of the hematopoietic stem cells. Not surprisingly, both morphological and functional abnormalities of megakaryocytes and platelets are common in these disorders.[97,98] These abnormalities may explain the increased risk for bleeding or thrombosis seen in these conditions.

In essential thrombocythemia elevated platelet counts (often above a million) are seen, sometimes with prolonged bleeding times. Typically, a diagnostically useful absence of platelet aggregation to epinephrine secondary to a deficiency of platelet α-adrenergic receptors can be observed.[99] In vitro aggregation to ADP and collagen are more variable. To a lesser degree polycythemia vera and agnogenic myeloid metaplasia may show a similar abnormality, whereas platelet dysfunction in chronic myelogenous leukemia is rarer.[100] Interestingly, clinically significant episodes of thrombosis or hemorrhage in these disorders do not correlate well with platelet counts, bleeding times or in vitro platelet aggregation tests.[101] The actual biochemical abnormalities in some of these disorders include deficiency in surface-related platelet receptors, in the surface connecting system, the dense tubular system and in platelet storage-pool granules. Abnormalities in arachidonic acid metabolism with decreased activity of the lipoxygenase and cyclo-oxygenase enzymes have also been reported.

Drugs.[57,58] In a dose of 200 mg, aspirin consistently and predictably doubles the bleeding time[102] by irreversibly inhibiting platelet cyclo-oxygenase.[103-105] The result is impaired thromboxane A_2 formation and a mild bleeding tendency. The platelet defect lasts for four to ten days after a single dose and is the result of irreversible acetylation of cyclo-oxygenase. As in congenital cyclo-oxygenase deficiency, the diagnosis is based on findings of impaired collagen-induced aggregation and the absence of second-phase aggregation to ADP and epinephrine in conjunction with a normal ATP to ADP ratio. If aspirin is given to

a patient with an independent hemostatic defect, such as thrombocytopenia or hemophilia, severe bleeding may result. In such cases the drug should be discontinued. In some instances (such as during surgical procedures), excessive bleeding resulting from dysfunctional platelets that were produced by earlier aspirin therapy may require platelet transfusion.

Other nonsteroidal anti-inflammatory drugs such as phenylbutazone, indomethacin, fenoprofen and ibuprofen are also capable of reversibly inhibiting platelet cyclo-oxygenase and impairing the mechanism of thromboxane A_2 generation.[104] Similar to the defect induced by aspirin therapy, the inability to generate thromboxane A_2 is the cause for impaired platelet release and aggregation. The bleeding time is slightly prolonged. Aspirin ingestion may cause easy bruising, menorrhagia and gastrointestinal bleeding.

The drug sulfinpyrazone, used in the secondary prevention of myocardial infarction, is becoming more widespread since the results of the Anturane Reinfarction Trial Group's[106] study have become available. Sulfinpyrazone and its metabolites inhibit cyclo-oxygenase and decrease platelet aggregation.[107] The drug has no effect on platelet adhesion and shortened platelet survival may be returned to normal. The mechanism of action of sulfinpyrazone in vivo, however, remains unknown, but it is important to note that ingestion of sulfinpyrazone does not impair platelet function in vivo, and no bleeding tendency is seen in patients taking this drug.

Nitrofurantoin prolongs the bleeding time by one to three minutes by inhibiting ADP-induced platelet aggregation and collagen-induced platelet release. The clinical significance of this effect is uncertain.[108]

Alcohol. Alcoholism is associated with significant abnormalities of platelets and of blood clotting.[109,110] In alcoholic patients without liver disease, high doses of alcohol induce a quantitative and qualitative defect of platelets. The qualitative abnormalities are multiple and include decreased platelet aggregation and release, decreased storage-pool ADP as well as decreased platelet procoagulant activity. Intake of large amounts of ethanol inhibits the rate of synthesis of prostaglandin endoperoxides and thus impairs thromboxane A_2 formation.[111] These changes are associated with abnormalities in platelet morphology at the ultrastructural level. The qualitative defect of platelet function superimposed on a variable degree of thrombocytopenia places the patient at additional risk of bleeding, which is even greater when the patient also has coagulation abnormalities associated with significant liver disease. The effect of alcohol on platelets is reversible.[109]

Evaluation of platelet function in a patient with alcoholism is but one aspect of the complete evaluation of hemostasis needed in such patients because of the complexity of the hemostatic defect so frequently seen. Thrombocytopenia with or without an associated qualitative platelet defect is treated with platelet transfusion of concentrates if the patient has significant bleeding.

Altered cAMP Metabolism

A number of drugs, especially the phosphodiesterase inhibitors and a number of prostaglandins are able to inhibit platelet function by elevating cAMP levels within platelets. Dipyridamole is a phosphodiesterase inhibitor that prevents the breakdown of cAMP[57,58,112] and thereby elevates the levels of this second messenger within platelets, making the platelets less likely to undergo aggregation and release when stimulated. It has been suggested that this is the mechanism of action of dipyridamole. It has also been suggested that prostaglandins such as prostacyclin (PGI_2) may potentiate the effect of dipyridamole on platelets because prostacyclin itself is also able to elevate cAMP levels in platelets. Pharmacologic doses of PGE_1 and PGD_2, acting through a common receptor also, elevate cAMP levels of platelets and thereby inhibit platelet aggregation and release both in vitro and in vivo. In the case of the prostaglandins, such platelet inhibitory activity may prolong the bleeding time and induce a mild hemostatic defect. It is postulated that the effects of these agents are mediated through specific membrane receptors, and that the resultant elevated cAMP level inhibits the ATP-dependent translocation of intracellular calcium; low levels of free calcium inhibit interaction of actin and myosin and, hence, impair platelet secretory activity.

Other Disorders

Platelet Procoagulant Activity

Platelets contribute significantly to the rapid early generation of fibrin by providing platelet surface phospholipid receptor sites for activated clotting factors Va and Xa, which bind to the

platelet surface and rapidly catalyse the conversion of prothrombin to thrombin. Fibrin formed by thrombin stabilizes the platelet aggregate and allows for the formation of a stable hemostatic plug. The complex interaction of platelet surface receptors and activated clotting factors has in the past been called platelet factor 3 activity. A patient with a congenital deficiency of receptors for factor Va has been described.[113,114] The patient had a normal bleeding time but had a significant history of menorrhagia and postoperative bleeding as well as easy bruising.

Heparin

Heparin is used in the treatment of venous thrombosis because of its inhibitory effect on coagulation.[115] It does not generally affect platelet function significantly as shown by the fact that the bleeding time remains normal following bolus injection of heparin. However, occasionally it may have a significant effect on platelets. In some patients heparin-induced thrombocytopenia develops, either as a result of an immunologic mechanism[116] or because of activation of platelets by a contaminating fraction in certain types of heparin preparation.[117]

Clinical Approach

The congenital disorders of platelet function have been studied extensively and have provided important insights into platelet physiology and pathophysiology; however, these defects are uncommon in clinical medicine. On the other hand, acquired syndromes of platelet dysfunction are more complex, less well studied, more difficult to classify, but occur frequently in a wide variety of clinical settings.

The severity of a bleeding disorder caused by platelet dysfunction depends not only on the nature of the platelet defect itself, but also on the severity of the hemostatic challenge. Disorders of platelet function vary in severity from the mild syndromes of easy bruisability seen, for example, in the storage-pool deficiencies, to the severe and sometimes fatal hemorrhages seen in such conditions as autosomal recessive von Willebrand disease. The bleeding tendency in any of the platelet function disorders may be aggravated by the introduction of additional hemostatic defects such as chemotherapy-induced thrombocytopenia or the administration of aspirin or anticoagulant drugs. Gastrointestinal or genitourinary bleeding may be a manifestation of defective platelet function; such bleeding may be precipitated by an underlying structural abnormality such as an ulceration or polyps of the colon or bladder.

The diagnostic approach to patients with platelet dysfunction should depend somewhat on the urgency with which the provisional diagnosis must be made in order to manage the bleeding diathesis. For example, the diagnostic workup of a patient with an acute bleeding episode may be limited to a screening test evaluation of hemostasis followed by a decision as to the possible role that a platelet defect may play in causing the bleeding. Because acute disorders are usually transient, comprehensive evaluation may not be possible. In contrast, the diagnostic workup in a patient with chronic or recurrent bleeding should be definitive. Most often the diagnosis can be suggested on the basis of information obtained in the history, physical examination and simple laboratory assessment; however, confirmation frequently requires diagnostic tests that are available only in specialized laboratories. In the case of a patient with a mild congenital bleeding disorder in whom von Willebrand disease has been excluded and for which there is not a specific therapy, there is greater flexibility in the time permitted for laboratory confirmation.

Approach to Diagnosis

The diagnosis of platelet dysfunction in most instances is made by the systematic analysis of information obtained in the history and physical examination and by laboratory evaluation of platelet function as well as of other aspects of hemostasis.[118]

Diagnostically, the most valuable data from a patient's history include (1) the onset, site, extent, severity and time course of bleeding episodes and the severity of the trauma that elicits such episodes; (2) a positive drug history; (3) a positive family history for bleeding tendencies and the pattern of bleeding in such family members, and (4) the presence of other illnesses that may be contributing factors in the disorder of platelet function.

On physical examination, the documentation of petechiae or purpura is suggestive of a defect in platelet plug formation. Because spontaneous gastrointestinal or genitourinary bleeding may in-

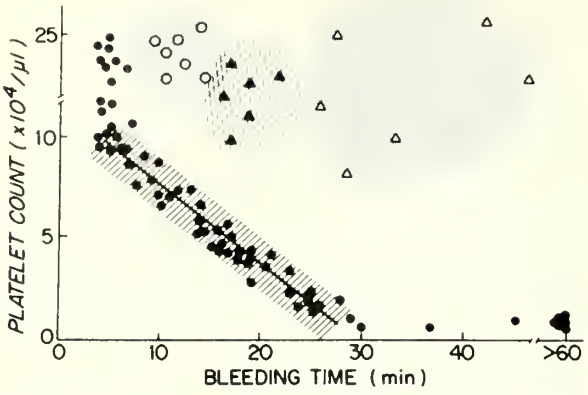


Figure 3.—Relationship of bleeding time to circulating platelet count in normal subjects and in patients with thrombocytopenia resulting from decreased production of platelets (closed circles). Platelet functional defects are also represented in subjects taking aspirin (open circles), in those with uremia (closed triangles) and in those with inherited von Willebrand disease (open triangles). (Reproduced with permission from Seminars in Hematology.)

dicate platelet dysfunction, the findings of guaiac-positive stools or hematuria may be important. Hemarthrosis and muscle hematomata are unusual manifestations of a qualitative defect of platelet function, except in severe von Willebrand disease, and generally suggest an alternative diagnosis such as hemophilia.[47] In patients in hospital with serious systemic illnesses, the presence of petechiae as well as oozing from surgical wounds, sites of trauma or venipuncture are important as evidence of defective platelet plug formation.

The screening laboratory evaluation of platelet function begins with a platelet count and a template bleeding time (Figure 3). The bleeding time is a simple, reproducible test of overall platelet function and has a normal range of 5.5 ± 1.5 minutes.[102,119] The bleeding time is significantly but variably prolonged in patients with a serious platelet function defect but adequate platelet counts. A qualitative abnormality superimposed on thrombocytopenia manifests as an inappropriately prolonged bleeding time for the degree of thrombocytopenia (Figure 3).

Light microscopic examination of a stained blood film may be useful. Large-appearing platelets may suggest the Bernard-Soulier syndrome, gray platelets are present in the gray platelet syndrome and pronounced platelet poikilocytosis may be seen in the myeloproliferative syndromes. Examination of the other formed elements of the blood may also be helpful.

In most situations of suspected platelet dysfunction a screening evaluation of the coagulation cascade is required. This consists of determining prothrombin time, partial thromboplastin time, thrombin time and amount of fibrinogen present. Many acquired disease states have an accompanying disorder of platelet function; therefore, the easiest way to make a diagnosis of a platelet dysfunction under such circumstances is to find a disproportionately prolonged bleeding time in a clinical situation in which platelet dysfunction is known to be relatively common.

Any patient with a history of abnormal bleeding and a prolonged bleeding time should be evaluated for the presence of VWD. The diagnosis is best established by the simultaneous measurements of FVIII:Co and FVIII:Ag. These measurements combined with a prolonged bleeding time and decreased platelet aggregation to ristocetin allow a diagnosis to be made in most patients with von Willebrand disease.[39]

Platelet aggregation is widely available for the evaluation of platelet function and may provide useful diagnostic information, especially in the congenital disorders of platelet function. For example, in vitro aggregation to ADP, epinephrine and collagen is absent with thrombasthenia and may be decreased in aspirin-like defects and storage-pool deficiencies. Ristocetin-induced aggregation is decreased to absent in most patients with von Willebrand disease or the Bernard-Soulier syndrome. Epinephrine fails to aggregate platelets in most patients with idiopathic thrombocythemia, a fact of some diagnostic use. Although in vitro testing of platelet aggregation may provide important diagnostic clues, the technique is difficult to reproduce and to standardize, and the abnormalities seen with such tests may have little or no relationship to the actual mechanism of the hemostatic defect in vivo.

Electron microscopy has been used in the enumeration of platelet δ-granules and α-granules to confirm storage-pool deficiencies.[120] Direct measurements of δ-granule ADP and ATP are required to differentiate storage-pool deficiencies from those like aspirin-caused defects. Platelet α-granule contents may be evaluated by measuring releasable pools of PF4 and β-TG by radioimmunoassay, tests that are now available commercially. Platelet arachidonic acid metabolism may be evaluated by measuring its stable end

product thromboxane B_2 using radioimmunoassay or by noting an absence of in vitro platelet aggregation to added arachidonic acid.

Management

Proper treatment of disorders of platelet function depends on an accurate diagnosis, and it varies from patient to patient and from disease to disease. Generally, treatment is directed at removing, if possible, the cause of the platelet dysfunction, such as treating systemic diseases like uremia or multiple myeloma and removing, if possible, drugs that may be causally implicated in platelet dysfunction syndromes. Immunosuppressive therapy may be indicated in immune-mediated dysfunction. In patients with platelet dysfunction resulting from deficiency of a required plasma cofactor such as von Willebrand disease, replacement therapy (for example, cryoprecipitate) is needed. If, on the other hand, an extrinsic factor acts as an inhibitor, as with plasma dysproteinemia, then replacement using platelet concentrates may be ineffective and removal of the inhibitor is necessary (for example, removal of a paraprotein by plasmapheresis). If the hemostatic disorder is due to an intrinsic platelet defect and the patient is bleeding, administration of platelet concentrates is indicated.

If both qualitative and quantitative platelet defects are present, the guidelines for use of platelet concentrates remain unclear. Patients have been shown to lose little blood if they have more than 5,000 per μl of normally functioning platelets and no underlying structural pathological condition (such as a colonic polyp or peptic ulcer).[76] Under such circumstances, prophylactic platelet concentrates are given only when the platelet count falls below 5,000 per μl. If, however, a qualitative defect is superimposed on a profound thrombocytopenia (as for example, carbenicillin therapy in a patient receiving pancytopenic chemotherapy), the risk of bleeding increases considerably and the recommendations of prophylactic platelet transfusions may be made at a platelet count of 20,000 per μl or more. If a patient is bleeding and this is due in whole or in part to a functional platelet defect, then platelet concentrates are indicated irrespective of the platelet count. Platelet concentrates should be used judiciously, however, because alloimmunization to platelets will develop, resulting in refractoriness to subsequently transfused platelet concentrates.[76] In such situations human leukocyte antigen (HLA)-typing and platelet cross-matching procedures are helpful in identifying compatible donors.[76,121]

REFERENCES

1. Baumgartner HR, Muggli R: Adhesion and aggregation: Morphological demonstration and quantitation in vivo and in vitro, *In* Gordon JL (Ed): Platelets in Biology and Pathology. Amsterdam, North-Holland, 1976, pp 23-60

2. Zucker MB: The functioning of blood platelets. Sci Am 242: 86-103, 1980

3. Harker LA, Ross R: Pathogenesis of arterial vascular disease. Sem Thrombos Hemostas 4:274-292, 1979

4. Mitchell JRA: Clinical events resulting from thrombus formation. Br Med Bull 34:103-106, 1978

5. Hardisty RM: Disorders of platelet function. Br Med Bull 33:207-212, 1977

6. Weiss HJ: Congenital disorders of platelet function. Sem Hematol 17:228-241, 1980

7. Caen JP, Cronsberg S, Cubisz P: Platelets: Physiology and Pathology. New York, Stratton International Medical Book Corp, 1977

8. Malpass TW, Harker LA: Acquired disorders of platelet function. Sem Hematol 17:242-258, 1980

9. White JG: Platelet morphology and function, *In* Williams WJ, Beutler E, Erslev AJ, et al (Eds): Hematology. New York, McGraw-Hill, 1977, pp 1159-1175

10. Holmsen H, Weiss HJ: Secretable storage pools in platelets. Ann Rev Med 30:119-134, 1979

11. Kaplan KL, Broekman MJ, Chernoff A, et al: Platelet alpha-granule proteins: Studies on release and subcellular localization. Blood 53:604-618, 1979

12. Crawford N, Taylor DG: Biochemical aspects of platelet behaviour associated with surface membrane reactivity. Br Med Bull 33:199-206, 1977

13. Weiss HJ: Platelet physiology and abnormalities of platelet function. N Engl J Med 293:531-541 and 580-588, 1975

14. Mustard JF, Packham MA: Normal and abnormal hemostasis. Br Med Bull 33:187-192, 1977

15. Baumgartner HR, Muggli R, Tschopp TB, et al: Platelet adhesion, release and aggregation in flowing blood: Effects of surface properties and platelet function. Thromb Hemostas 35: 124-138, 1976

16. Sakariassen KS, Bolhuis PA, Sixma JJ: Human blood platelet adhesion to artery subendothelium is mediated by factor VIII —von Willebrand factor bound to the subendothelium. Nature 279:636-638, 1979

17. Santoro SA, Cunningham LW: Fibronectin and the multiple interaction model for platelet-collagen adhesion. Proc Natl Acad Sci USA 76:2644-2648, 1979

18. Nurden AT, Caen JP: The different glycoprotein abnormalities in thrombasthenia and Bernard-Soulier platelets. Sem Hematol 16:224-250, 1979

19. Phillips DR: Membrane glycoproteins mediating platelet aggregation, *In* Mann KG, Taylor FB (Eds): The Regulation of Coagulation. New York, Elsevier, 1980, pp 259-270

20. Burch JW, Majerus PW: The role of prostaglandins in platelet function. Sem Hematol 16:196-207, 1979

21. Shick PK: The role of platelet membrane lipids in platelet hemostatic activities. Sem Hematol 16:221-233, 1979

22. Coller BS: Interaction of normal thrombasthenic, and Bernard-Soulier platelets with immobilized fibrinogen: Defective platelet--fibrinogen interaction in thrombasthenia. Blood 55:169-177, 1980

23. Kinlough-Rathbone RL, Packham MA, Reimers H-J, et al: Mechanisms of platelet shape change, aggregation, and release by collagen, thrombin or A23, 187. J Lab Clin Med 90:707-719, 1977

24. Majerus PW, Millotich JP, Kane WH, et al: The formation of thrombin on platelet surface, *In* Mann KG, Taylor FB (Eds): The Regulation of Coagulation. New York, Elsevier, 1980, pp 215-224

25. White JG, Rao GHR, Gerrard JM: Platelet stimulus activation contraction secretion coupling: A frequently fractured chain of events, *In* Mann KG, Taylor FB (Eds): The Regulation of Coagulation. New York, Elsevier, 1980, pp 363-376

26. Hathaway DR, Eaton CR, Adelstein RS: Regulation of human platelet myosin kinase by calcium—calmodulin and cyclic AMP. *In* Mann KG, Taylor FB (Eds): The Regulation of Coagulation. New York, Elsevier, 1980, pp 271-276

27. Moncada S, Vane JR: Arachidonic acid metabolites and the interactions between platelets and blood-vessel walls. N Engl J Med 300:1142-1147, 1979

28. Gerrard JM, White JG: Prostaglandins and thromboxanes: "Middlemen" modulating platelet function in hemostasis and thrombosis. Prog Hemost Thromb 4:87-125, 1978

29. Bell RL, Majerus PW: Thrombin-induced hydrolysis of phosphatidylinositol in human platelets. J Biol Chem 255:1790-1792, 1980

30. Burch JW, Stanford N, Majerus PW: Inhibition of platelet prostaglandin synthetase by oral aspirin. J Clin Invest 61:314-319, 1978

31. DiMinno G, Silver MJ, DeGaetano G: Prostaglandins as inhibitors of human platelet aggregation. Br J Hematol 43:632-647, 1979

32. Pinnell SR: Disorders of collagen, *In* Stanbury JB, Wyngaarden JB, Fredrickson DS (Eds): The Metabolic Basis of Inherited Disease. New York, McGraw-Hill, 1978, pp 1366-1394

33. Weary PE, Wheeler CE, Canley EP: Adult scurvy. Arch Dermatol 83:657-659, 1961

34. Crandon JH, Lund CC, Dill DB: Experimental human scurvy. N Engl J Med 223:353-369, 1940

35. Glenner GG: Amyloid deposits and amyloidosis. The β-fibrilloses. N Engl J Med 302:1283-1292 and 1333-1343, 1980

36. Brownstein MH, Helwig EB: The cutaneous amyloidosis. Arch Dermatol 102:20-28, 1970

37. Greipp PR, Kyle RA, Bowie EJW: Factor X deficiency in primary amyloidosis: Modulation after splenectomy. N Engl J Med 301:1050-1051, 1979

38. Weiss HJ, Tschopp TB, Baumgartner HR, et al: Decreased adhesion of giant (Bernard-Soulier) platelets to subendothelium: Further implications on the role of the von Willebrand factor in hemostasis. Am J Med 57:920-925, 1974

39. Hoyer LW: Von Willebrand's disease. Prog Hemost Thromb 3:231-287, 1976

40. Miller CH, Graham JB, Goldin LR, et al: Genetics of classic von Willebrand's disease—I. Phenotypic variation within families. Blood 54:117-136, 1979

41. Italian Working Group: Spectrum of von Willebrand's disease: A study of 100 cases. Br J Haematol 35:101-112, 1977

42. Salzman EW: Measurement of platelet adhesiveness: A simple in vitro technique demonstration on abnormality in von Willebrand's disease. J Lab Clin Med 62:724-735, 1963

43. Gralnick HR, Sultan Y, Coller BS: Von Willebrand's disease: Combined qualitative and quantitative abnormalities. N Engl J Med 296:1024-1025, 1977

44. Zimmerman TS, Abildgaard CF, Meyer D: The factor VIII abnormality in severe von Willebrand's disease. N Engl J Med 301:1307-1310, 1979

45. Tschopp TB, Weiss HJ, Baumgartner HR: Decreased adhesion of platelets to subendothelium in von Willebrand's disease. J Lab Clin Med 83:296-300, 1974

46. Weiss HJ, Baumgartner HR, Tschopp TC, et al: Correction by factor VIII of the impaired platelet adhesion to subendothelium in von Willebrand's disease. Blood 51:267-279, 1978

47. Rizza CR: Von Willebrand's disease, *In* Biggs R (Ed): The Treatment of Haemophilia A and B and von Willebrand's Disease. Oxford, Blackwell Scientific Publications, 1978, pp 172-180

48. Ruggeri FM, Pareti FI, Mannucci PM, et al: Heightened interaction between platelets and factor VIII/von Willebrand factor in a new subtype of von Willebrand's disease. N Engl J Med 302:1047-1051, 1980

49. Nilsson IM, Bergentz S-E, Larsson SA: Surgery in von Willebrand's disease. Ann Surg 190:746-752, 1979

50. Ingram GIC, Prentice CRM, Forbes CD, et al: Low factor VIII-like antigen in acquired von Willebrand's syndrome and response to treatment. Br J Haematol 25:137-140, 1973

51. Handin RI, Martin V, Moloney WC: Antibody-induced von Willebrand's disease: A newly defined inhibitor syndrome. Blood 48:393-405, 1976

52. Joist JH, Cowan JF, Zimmerman TS: Acquired von Willebrand's disease. N Engl J Med 298:988-991, 1978

53. Meyer D, Frammel D, Larrien MJ, et al: Selective absence of large forms of factor VIII/von Willebrand factor in acquired von Willebrand's syndrome—Response to transfusion. Blood 54: 600-606, 1979

54. Castaldi PA, Rozenberg MC, Stewart JA: The bleeding disorder of uraemia—A qualitative platelet defect. Lancet 2:66-69, 1966

55. Steiner RW, Coggins C, Carvallho ACA: Bleeding time in uremia: A useful test to assess clinical bleeding. Am J Hematol 7:107-117, 1979

56. Horowitz HI, Stein IM, Cohen BD: Further studies on the platelet-inhibiting effect of guanidino succinic acid and its role in uremic bleeding. Am J Med 49:336-345, 1970

57. Packham MA, Mustard JF: Clinical pharmacology of platelets. Blood 51:555-573, 1977

58. Wautier JL, Caen JP: Pharmacology of platelet-suppressive agents. Sem Thromb Hemost 5:293-315, 1979

59. Kinlough-Rathbone RL, Groves HM, Cazenave J-P, et al: Effect of dipyridamole and aspirin in platelet adherence to damaged rabbit aortas in vitro and in vivo. Fed Proc 37:260, 1978

60. Harker LA, Hanson SR: Experimental arterial thromboembolism in baboons—Mechanism, quantitation and pharmacologic prevention. J Clin Invest 64:559-569, 1979

61. Moncada S, Korbut R: Dipyridamole and other phosphodiesterase inhibitors act as antithrombotic agents by potentiating endogenous prostacyclin. Lancet 1:1286-1289, 1978

62. Sullivan JM, Harken DE, Gorlin R: Pharmacologic control of thromboembolic complications of cardiac-valve replacement. N Engl J Med 284:1391-1394, 1971

63. The Persantine Aspirin Reinfarction Study Research Group: Persantine and aspirin in coronary heart disease. Circulation 62: 449-461, 1980

64. Caen J, Castaldi PA, Leclerc JC, et al: Congenital bleeding time and normal platelet count—I. Glanzmann's thrombasthenia (report of 15 patients). Am J Med 41:4-26, 1966

65. Caen JP: Glanzmann's thrombasthenia. Clin Hematol 1: 383-392, 1972

66. McEver RP, Baenziger NL, Majerus PW: Isolation and quantitation of the platelet protein lacking in thrombasthenia using a monoclonal hybridoma antibody. Clin Res 28:495A, 1980

67. Weiss HJ, Rogers J: Fibrinogen and platelets in the primary arrest of bleeding: Studies in 2 patients with congenital afibrinogenemia. N Engl J Med 285:369-374, 1971

68. Sharp AA: Diagnosis and management of disseminated intravascular coagulation. Br Med Bull 33:265-272, 1977

69. Orloff KG, Michaeli D: Inhibition of fibrin-platelet interactions by fibrinogen-degradation fragment D. Am J Physiol 233: H305-H311, 1977

70. Deutsch E: The liver and blood clotting. Sem Thromb Hemost 4:1-82, 1977

71. Perkins HA, MacKenzie MR, Fudenberg HH: Hemostatic defects in dysproteinemias. Blood 35:695-707, 1970

72. Clagett GP, Salzman EW: Prevention of venous thromboembolism. Prog Cardiovasc Dis 17:345-366, 1975

73. Weiss HJ: The effect of clinical dextran on platelet aggregation, adhesion and ADP release in man: in vitro and in vivo studies. J Lab Clin Med 69:37-46, 1967

74. Brown III CH, Natelson EA, Bradshaw, MW, et al: The hemostatic defect produced by carbenicillin. N Engl J Med 291: 265-270, 1974

75. Shattil SJ, Bennett JS, McDonough M, et al: Carbenicillin and penicillin G inhibit platelet function in vitro by impairing the interaction of agonists with the platelet surface. J Clin Invest 65: 329-337, 1980

76. Slichter SJ, Harker LA: Thrombocytopenia: mechanisms and management of defects in platelet production. Clin Hematol 7:523-539, 1978

77. Raccuglia G: Gray platelet syndrome: a variety of qualitative platelet disorders. Am J Med 51:818-828, 1971

78. Gerrard JM, Philips DR, Rao GH, et al: Biochemical studies of two patients with the gray platelet syndrome—Selective deficiency of platelet alpha granules. J Clin Invest 66:102-109, 1980

79. Harker LA, Malpass TW, Branson HE, et al: Mechanism of abnormal bleeding in patients undergoing cardiopulmonary bypass: Acquired transient platelet dysfunction associated with selective α-granule release. Blood 56:824-834, 1980

80. Bick, RL: Alteration of hemostasis associated with cardiopulmonary bypass: Pathophysiology, prevention, diagnosis and management. Sem Thromb Hemost 3:59-82, 1976

81. Holmsen H, Weiss HJ: Further evidence for a deficient storage pool of adenine nucleotides in platelets from some patients with thrombocytopathia—"Storage pool disease." Blood 39:197-209, 1972

82. Weiss HJ, Witte LD, Kaplan KL, et al: Heterogeneity in storage pool deficiency: Studies on granule bound substances in 18 patients including variants deficient in α-granules, platelet factor 4, β-thromboglobulin, and platelet-derived factor. Blood 54:1296-1319, 1979

83. Clancy RL, Jenkins E, Firkin B: Qualitative platelet abnormalities in idiopathic thrombocytopenic purpura. N Engl J Med 286:622-626, 1972

84. Russel NH, Keenan JP: Thrombocytopathy associated with autoimmune hemolytic anemia. Br Med J 2:604, 1978

85. Karpatkin S, Lackner HL: Association of antiplatelet antibody with functional platelet disorders. Autoimmune thrombocytopenic purpura systemic lupus erythematosus and thrombopathia. Am J Med 59:599-604, 1975

86. Zahavi J: Acquired "storage pool disease" of platelets. Thromb Hemost (Stugg) 35:501-507, 1976

87. Czapek EE, Deykin D, Salzman E, et al: Intermediate syndrome of platelet dysfunction. Blood 52:103-113, 1978

88. Malmsen C, Hamberg M, Svensson J, et al: Physiological role of an endoperoxide in human platelets: Hemostatic defect due to platelet cyclooxygenase deficiency. Proc Natl Acad Sci USA 72:1446-1448, 1975

89. Lagarde M, Byron PA, Vargaftig BB, et al: Impairment of platelet thromboxane A_2 generation and of the platelet release reaction in two patients with congenital deficiency of platelet cyclooxygenase. Br J Hematol 38:251-266, 1978

90. Weiss HJ, Lages BA: Possible congenital defect in platelet thromboxane synthetase. Lancet 2:760-761, 1977

91. Mestel F, Oetliker O, Beck E, et al: Severe bleeding association with thromboxane synthetase. Lancet 1:157, 1980

92. Dyerberg J, Bang HO: Haemostatic function and platelet polyunsaturated fatty acids in Eskimos. Lancet 2:433-435, 1979

93. Siess W, Scherer B, Bohlig B, et al: Platelet-membrane fatty acids, platelet aggregation and thromboxane formation during a mackerel diet. Lancet 1:441-444, 1980

94. Cowan DH, Graham RC Jr, Baunach D: The platelet defect in leukemia—Platelet ultrastructure, adenine nucleotide metabolism, and the release reaction. J Clin Invest 56:188-200, 1975

95. Russell NH, Kennan JP, Bellingham AJ: Thrombocytopathy in preleukemia: Association with a defect of thromboxane A_2 activity. Br J Haematol 41:417-425, 1979

96. Lisiewicz J: Mechanisms of hemorrhage in leukemia. Sem Thromb Hemostasis 4:241-267, 1978

97. Cardamone JM, Edson JR, McArthur JR, et al: Abnormalities of platelet function in the myeloproliferative disorders. JAMA 221:270-273, 1972

98. Murphy S, Davis JL, Walsh PN, et al: Template bleeding time and clinical hemorrhage in myeloproliferative disease. Arch Intern Med 138:1251-1253, 1978

99. Kaywin P, McDonough M, Insel PA, et al: Platelet function in essential thrombocythemia. N Engl J Med 299:505-509, 1978

100. Gerrard JM, Stoddard SF, Shapiro RS, et al: Platelet storage pool deficiency and prostaglandin synthesis in chronic granulocytic leukemia. Br J Haematol 40:597-607, 1978

101. Boughton BJ, Corbett WEN, Ginsberg AD, et al: Myeloproliferative disorders: Paradox of in vivo and in vitro platelet function. J Clin Pathol 30:228-234, 1977

102. Mielke Jr CH, Kanehiro MM, Maher IA, et al: The standardized normal Ivy bleeding time and its prolongation by aspirin. Blood 34:204-215, 1969

103. Vane JR: Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nature (New Biol) 231: 232-235, 1971

104. Moncada S, Vane JR: Mode of action of aspirin-like drugs. Adv Intern Med 24:1-22, 1979

105. Roth GJ, Stanford N, Majerus PW: Acetylation of prostaglandin synthetase by aspirin. Proc Natl Acad Sci USA, 72:3073-3076, 1975

106. The Anturane Reinfarction Trial Research Group: Sulfinpyrazone in the prevention of sudden death after myocardial infarction. N Engl J Med 302:250-255, 1980

107. Ali M, McDonald JWD: Effects of sulfinpyrazone on platelet prostaglandin synthesis and platelet release of serotonin. J Lab Clin Med 89:868-875, 1977

108. Rossi EC, Levin NW: Inhibition of primary ADP-induced platelet aggregation in normal subjects after administration of nitrofurantoin (Furadantin). J Clin Invest 52:2457-2467, 1973

109. Cowan DH: Effect of alcoholism on hemostasis. Sem Hematol 17:137-147, 1980

110: Haut MJ, Cowan DH: The effect of ethanol in hemostatic properties of human blood platelets. Am J Med 56:22-33, 1974

111. Stuart MJ: Ethanol-inhibited platelet prostaglandin synthesis in vitro. J Studies Alcohol 40:1-6, 1979

112. Michel H, Caen JP, Burn GUR, et al: Relation between the inhibition of aggregation and the concentration of cAMP in human and rat platelets. Br J Hematol 33:27-38, 1976

113. Miletich JP, Kane WH, Hofmann SL, et al: Deficiency of factor X_a-factor V_a binding sites on the platelets of a patient with a bleeding disorder. Blood 54:1015-1022, 1979

114. Weiss HJ, Vicic WJ, Lages BA, et al: Isolated deficiency of platelet procoagulant activity. Am J Med 67:206-213, 1979

115. Rosenberg RD: Biologic actions of heparin. Sem Hematol 14:427-440, 1977

116. Babcock RB, Dumper CW, Scharfman WB: Heparin-induced immune thrombocytopenia. N Engl J Med 295:237-241, 1976

117. Salzman EW, Rosenberg RD, Smith MH, et al: Effect of heparin fractions on platelet aggregation. J Clin Invest 65:64-73, 1980

118. Ingram GIC: Investigation of a longstanding bleeding tendency. Br Med Bull 33:261-264, 1977

119. Harker LA, Slichter SJ: The bleeding time as a screening test for evaluation of platelet function. N Engl J Med 287:155-159, 1972

120. Weiss HJ, Ames RP: Ultrastructural findings in storage pool disease and aspirin-like defects of platelets. Am J Pathol 71: 447-458, 1973

121. Slichter SJ: Controversies in platelet transfusion therapy. Ann Rev Med 31:509-540, 1980

Specialty Conference

Refer to: Schrier SL, Sasahara AA, Wall RT, et al: The use of fibrinolytic agents—Stanford University School of Medicine (Specialty Conference). West J Med 134:128-133, Feb 1981

Moderator
STANLEY L. SCHRIER, MD

Participants
ARTHUR A. SASAHARA, MD
ROBERT T. WALL, MD
CHRISTINA B. HARBURY, MD

An edited transcription of a Conference held at Stanford University Medical Center, Stanford, California. This transcript has been edited by Robert T. Wall, MD.

The Use of Fibrinolytic Agents

STANLEY L. SCHRIER, MD:* *To allow for informed opinion on the clinical use of the new, potent fibrinolytic agents streptokinase and urokinase, we have organized this program on the pharmacology and mechanism of action of these drugs. We will end with a proposal for the clinical use of these agents. Dr. Arthur Sasahara from the Harvard Medical School will review the basic physiology and mode of action of these agents and then will report the clinical experience with these drugs. Dr. Robert Wall from our division will discuss certain aspects of arterial and venous thromboembolism, discussing those circumstances where fibrinolytic therapy might be indicated. We will end with Dr. Christina Harbury, also of our division, who will discuss the hemorrhagic consequences of these agents, plus a consideration of what role the Clinical Coagulation Laboratory might have in drug monitoring.*

ARTHUR A. SASAHARA, MD:† My job this morning is to discuss the data and evidence supporting the recommendation that lytic therapy now be used as primary therapy in the appropriate clinical situation of venous thromboembolism. The data that I will discuss today were obtained from two National Institutes of Health trials, the phase I trial—the Urokinase Pulmonary Embolism Trial (UPET), a comparison of the efficacy of clot resolution between conventional heparin therapy and urokinase therapy—and the phase II trial—the Urokinase-Streptokinase Pulmonary Embolism Trial (USPET), which was a study comparing urokinase with streptokinase. This study was needed because of the worldwide literature on streptokinase therapy which had accumulated before the investigation of urokinase. In addition, I will present some data obtained from splinter studies which we carried out in conjunction with these two national trials.

The administration of streptokinase or urokinase is simply the administration of exogenous activators of the natural fibrinolytic system, which results in the generation of plasmin from circulating plasminogen. These agents do not have direct thrombolytic activity. In the actual clinical situation, one would believe that in cases of massive thrombosis the body's own fibrinolytic system would be maximally activated, yet if one measured plasminogen or made other tests of fibrinolysis, one could not distinguish between health and disease states. This seeming deficit in the biofeedback mechanism of the natural lytic system permits the

*Head, Division of Hematology, Department of Medicine, Stanford University School of Medicine.

†Chief, Medical Service, West Roxbury Veterans Administration Medical Center, and Professor of Medicine, Harvard Medical School, Boston.

From the Division of Hematology, Department of Medicine, Stanford University School of Medicine, Stanford, California.

Reprint requests to: Robert T. Wall, MD, Division of Hematology, S-161, Department of Medicine, Stanford University School of Medicine, Stanford, CA 94305.

administration of urokinase or streptokinase to maximally activate the fibrinolytic system for clot dissolution.

What is the evidence that this form of therapy is worthwhile? In the phase I and phase II trials there were three end points used to judge drug efficacy. The first and most sensitive in judging clot resolution were serial pulmonary angiograms obtained before and 24 hours after therapy, which showed that the amount of clot lysis obtained with thrombolytic therapy was significantly greater than that obtained with conventional heparin therapy. In the phase II trial, streptokinase therapy resulted in essentially the same degree of clot resolution as with urokinase. The degree of clot resolution with heparin therapy was minimal within the first 24 hours. In patients with massive pulmonary embolism, defined as the obstruction of two or more lobar arteries, the results of thrombolytic therapy were particularly striking. As a result, the recommendation has been made that lytic therapy be used primarily in patients with massive embolism.

The second objective means used to assess drug efficacy were serial perfusion lung scans, and in the phase II trial, the improvement in reperfusion with 12 or 24 hours of urokinase or 24 hours of streptokinase administration was essentially the same. All three regimens were superior to heparin.

The third end point assessment used to judge drug efficacy consisted of serial measurements of eight hemodynamic variables from the right side of the heart and the pulmonary circulation. In the phase I trial, six of the eight measurements showed greater improvement in those who had received urokinase compared with those receiving heparin. These comparisons showed significant lowering of mean right atrial, right ventricular systolic, right ventricular end-diastolic and mean pulmonary arterial pressures, lowering of pulmonary vascular resistance and improvement in arterial oxygen tensions. In the phase II trial, comparing streptokinase with urokinase, comparable improvements were observed. These data show that therapy for 12 or 24 hours with urokinase or for 24 hours with streptokinase yield comparable clinical benefit.

In 85 percent to 90 percent of the patients in the trials, the lung scan findings had returned to normal or showed only a small, residual defect after a year. But because neither a lung scan nor a pulmonary angiogram is able to detect accurately damage in the pulmonary microcirculation (important in gas exchange), we measured the pulmonary capillary blood volume and diffusing capacity. We selected only those patients who were previously normal, excluding those with heart or lung disease which may independently damage the pulmonary microcirculation. Therefore, in the recovery period just before discharge, pulmonary function tests, diffusing capacity and pulmonary capillary blood volume measurements were made. These measurements were repeated after a year, following careful anticoagulation therapy.

The findings on pulmonary function tests were normal, confirming the absence of lung disease in both the heparin- and lytic-treated groups. However, the pulmonary capillary blood volume was abnormally low in the heparin-treated patients, whereas those who received lytic therapy had a mean value which was within the normal range. These data indicated to us that there was more complete clearing of thromboemboli from the pulmonary microcirculation when thrombolytic therapy had been employed.

A second splinter study concerned the source of thrombi. The fact that only a third of patients in most series will have clinical symptoms and signs of thrombophlebitis was a previous deterrent to the recognition of the strong relationship between thrombophlebitis of the deep leg veins and pulmonary embolism. But about 20 years ago Sevitt noted that patients who died of massive pulmonary embolism invariably had clots in the deep venous system, identified by careful dissection of the legs. Subsequently, Kakkar showed that whenever pulmonary embolism occurred in his postoperative patients, the radioactive fibrinogen tests, or leg scans, gave positive findings in the deep veins of the leg. To corroborate these observations we employed impedance plethysmography, a noninvasive technique to objectively assess the deep venous system. The test has been shown to have a sensitivity of 97 percent and a specificity of 93 percent in the detection of deep vein thrombosis. In 32 patients, 16 randomly assigned to the heparin group and 16 to the thrombolytic group, all of whom had abnormal impedance measurements, daily measurements were made. In one of the patients in the heparin group the abnormal impedance was converted to normal within 24 hours, indicating that there was no longer a venous outflow obstruction, whereas

in 11 of 16 patients in the lytic group impedance plethysmograms improved or became normal. At the end of a week, findings had become normal in three additional patients in the heparin group for a total of 4 (25 percent), whereas findings had become normal in one additional patient in the lytic-treated group for a total of 12 (75 percent).

In summary, these data show that thromboemboli are more completely resolved by lytic therapy than by heparin, when assessed by angiography, lung scanning and measurement of pulmonary capillary blood volume. In addition, the rapid lysis of clots in the deep venous system is also beneficial, based upon other observations that rapid lysis of clots in the deep venous system tends to preserve the anatomy and function of the venous valve cusps. It is also known that the slow, natural evolution of deep vein thrombi under conventional heparin therapy results in distortion and destruction of the valve cusps. It seems desirable, therefore, to employ thrombolytic therapy to prevent or to minimize the valve destruction which may lead to a postphlebitic leg syndrome.

A very pertinent issue is the risk involved in achieving these benefits. Bleeding is the only significant complication of lytic therapy and was observed more often in the lytic group than in the heparin-treated patients. On closer scrutiny, most of the bleeding occurred at sites where invasive procedures were carried out: cutdowns for pulmonary arterial catheters that were left in place, arterial punctures and multiple venipunctures. However, if invasive procedures are avoided or minimized, as in Bell's or our series, bleeding can be minimized to an incidence of 6 percent or less.

Other complications of lytic therapy include mild fever and some allergic reactions. Streptokinase caused a fever of more than 1.5°F in about 25 percent of patients while the incidence was less with urokinase. The allergic reactions were minor and occurred in about 6 percent of patients receiving streptokinase. One would not expect an allergic reaction with urokinase, which is a human protein. There was one patient who had a mild anaphylactic reaction with transient hypotension. In practice, when administering streptokinase, pretreatment with 100 mg of hydrocortisone is useful in preventing minor reactions.

No difference in mortality was noted among the heparin and lytic therapy groups. Mortality at two weeks was 8 percent and 15 percent at six months. However, six of the seven deaths in the heparin-treated group occurred because the patients never recovered from the initial cardiopulmonary insult caused by the pulmonary embolism. In the lytic therapy group, there were six deaths and only one was due to the initial pulmonary embolic event. The other deaths were related to bleeding, particularly cerebral hemorrhage. The strong recommendation now is that a pathologic cerebral process or anything related to instability of the cerebral circulation within two months is a major contraindication to the administration of thrombolytic therapy.

In summary, we believe—on the basis of the data from the two National Institutes of Health trials and on small studies reported here—that thrombolytic therapy is now a proven form of therapy which should be considered in all patients with significant pulmonary embolism.

DR. SCHRIER: *Dr. Robert Wall of the Division of Hematology would like to review now the basic biology of venous and arterial thrombosis.*

ROBERT T. WALL, MD:* In the next few minutes I would like to place into perspective the use of these fibrinolytic agents by discussing the mechanisms underlying arterial and venous thrombosis. Thrombosis is the consequence of exposure of blood to a damaged vessel wall. It is likely that arterial thrombosis is a consequence of loss or dysfunction of the thromboresistant endothelial cell layer which lines the vessel lumen. Platelets are consumed in this process and generally there is little fibrin generated. It is unlikely that fibrinolytic therapy will be useful in this setting. However, there are data now to suggest that in selected patients with acute myocardial infarction, selective infusion of these drugs into the obstructed coronary artery is effective in restoring blood flow to the myocardium. In venous thrombosis, both fibrinogen and platelets are consumed. The platelet consumption may be a passive accompaniment to the generation of the fibrin meshwork within these low shear vessels. Fibrinolytic therapy in this setting is on a solid theoretic foundation.

The clinical use of these agents has been reviewed by Dr. Sasahara. It is important to remember, however, that it is possible to identify groups who are at increased risk of venous throm-

*Assistant Professor, Division of Hematology, Department of Medicine, Stanford University School of Medicine.

bosis and that prophylactic therapy, such as low doses of heparin or stimulation of calf muscles, can be effective. Therefore, the number of patients who are candidates for lytic therapy should be small at any institution.

The bleeding induced by fibrinolytic therapy is due to depletion of clotting factors and lysis of recently formed hemostatic plugs. Bleeding may also occur up to several weeks after a surgical procedure. Further, fibrinolytic agents generate fibrin degradation products that can inhibit the polymerization of fibrin monomer and further compromise the ability to achieve hemostasis. These products also interfere with the formation of the platelet part of this hemostatic plug.

In summary, fibrinolytic agents are a potentially dangerous adjunctive therapy in the treatment of venous thrombotic disease. Preventive measures and anticoagulant therapy with heparin and orally given anticoagulants for established venous thrombosis remain the mainstays of therapy in this disease.

DR. SCHRIER: *We will now hear from Dr. Christina Harbury who is head of our Clinical Coagulation Laboratory. She will discuss some of the hemorrhagic complications of these agents and the use of the tests proposed for monitoring the drugs. She will also discuss the treatment of bleeding due to lytic therapy.*

CHRISTINA B. HARBURY, MD:* Lytic therapy induces a potential bleeding state. The bleeding is primarily associated with patients in whom invasive procedures have been carried out, but there is also significant incidence of spontaneous bleeding. What should you do when a patient bleeds? One unsupported recommendation is to double the dose of the lytic agent with the intent of depleting all the plasma plasminogen. However, most physicians simply stop the agents and give 1 unit of fresh frozen plasma.

Coagulation laboratory tests cannot predict bleeding. Tests that have been recommended to follow the effectiveness of the lytic therapy are the thrombin time, fibrinogen level and the euglobulin lysis test. Firm statements about the use of these tests during lytic therapy cannot be made because there are no clinical studies that address this point. To decrease the incidence of bleeding it is important not only to avoid unnecessary invasive procedures but also to avoid all drugs that impair platelet function. The most frequently offending drug is aspirin (acetylsalicylic acid) and aspirin-containing drug combinations.

DR. SCHRIER: *Let us deal first with the problem of serious bleeding. Do we stop administering the drug, do we give fresh frozen plasma? Some of the drug handouts indicate there is a potential use for epsilon aminocaproic acid, but I have not seen any reports in the literature about the efficacy of these agents. What does one do in the face of fibrinolytic hemorrhage?*

DR. SASAHARA: One can conveniently categorize the bleeding complications into mild and severe. Mild blood losses are treated by mechanical compression. In this regard it is important that any vascular puncture be confined to readily compressible vessels, usually the arm. We do not use aminocaproic acid. The half-life of the lytic agents is about 15 minutes and so, with moderate to severe bleeding, we recommend discontinuing administration of the drug. If the bleeding is general, we administer fresh frozen plasma or whole blood which rapidly reverses the lytic state.

Another question is that of time delay before giving heparin after completing lytic therapy. We follow the thrombin time and prefer to have it shorter than twice normal before starting heparin. In practice, this means waiting about two hours after lytic therapy is complete.

DR. SCHRIER: *I would like to summarize what we have heard this morning. There are now available in this country for clinical use two very effective thrombolytic agents. I think there is no question about their ability to lyse clots. The two agents are urokinase, which is expensive but nonallergenic, being a human protein, and streptokinase, which is a foreign protein and has a certain degree of allergic reactions associated with it. This latter drug is less expensive. There are two clinical trials on which much of the current therapeutic recommendations are based. These trials could be interpreted as showing no benefit by these agents because the death rate was not reduced—seven patients died in the heparin group in the* UPET *trial, and six in the lytic therapy group. Nevertheless, the participants in that trial were very impressed by some of the hemodynamic changes observed as well as the occasional dramatic change seen in individual patients. Further,*

*Head, Clinical Coagulation Laboratory, Division of Hematology, Department of Medicine, Stanford University School of Medicine.

they noted that of the six deaths in the fibrinolytic trial, five were due to hemorrhage. The implication, therefore, is that if one can prevent serious hemorrhagic complications, one could improve outcome. That is presumedly the basis on which these materials were then released.

Streptokinase is approved for use in massive pulmonary embolism or submassive pulmonary embolism, particularly with hemodynamic abnormalities, treatment of deep venous thrombosis, maintaining the patency of vascular access devices and shunts. With regard to urokinase, it is cleared only for use in massive or submassive pulmonary embolism. We are told this is a useful agent in the treatment of pulmonary embolism not only because it clears the pulmonary clots more quickly but, as Dr. Sasahara explained, there may be a long-range beneficial effect on the pulmonary vasculature. These are data we are interested in and need to see more of. With regard to the potential use in deep venous thrombosis, there are some data that suggest that the use of fibrinolytic agents may clear the clot more rapidly than occurs with heparin therapy and that rapid clearance may preserve the valve cusps and might thereby decrease the incidence of the postphlebitic syndrome.

There appears to be no documented evidence that aminocaproic acid is useful in the treatment of bleeding due to these drugs. There is some evidence that fresh frozen plasma will reverse the hemorrhagic state in a reasonable period of time.

A PHYSICIAN: What is the cost of using these agents in pulmonary embolism?

DR. SASAHARA: A very good question. The clinical efficacies are essentially identical. And I suppose some of it may come down to economics. The cost of streptokinase in treating pulmonary embolism is about $275. Urokinase for pulmonary embolism is ten times that amount. I think this may be a factor in drug selection, but there will also be 10 percent of patients who may not respond to streptokinase because of previous buildup of streptococcal antibodies. You will know this when you do the appropriate tests for demonstrating lytic state, the thrombin time and the euglobulin lysis time studies, in which case you may need to substitute urokinase.

A PHYSICIAN: Have these drugs been tried for in situ thrombosis in the pulmonary arteries as in sickle cell disease?

DR. SASAHARA: We have several patients in whom we have used it in that clinical situation. I cannot recall at this moment whether it caused dramatic improvement.

A PHYSICIAN: Dr. Sasahara, will you restate your summary of the effect of lytic therapy on pulmonary diffusing capacity?

DR. SASAHARA: Yes, the diffusing capacity in the recovery period in those patients without underlying heart-lung disease was abnormal in those treated with heparin; it was normal in those treated with lytic therapy. And since the membrane portion of diffusion was identical in both groups, the abnormality of the diffusing capacity was because of pulmonary capillary obstruction.

A PHYSICIAN: Did it become normal later?

DR. SASAHARA: We have data for six months and the difference has been maintained.

A PHYSICIAN: Dr. Wall, you commented on the difference between arterial and venous thrombosis. What about clots in the atria?

DR. WALL: The thrombi formed there are composed of fibrin and platelets and anticoagulation with warfarin is effective therapy.

A PHYSICIAN: What about thrombi in the left ventricle, or thromboembolism due to prosthetic valves?

DR. WALL: Antiplatelet agents will correct shortened platelet survival due to an artificial aortic valve. The therapeutic effect is increased when these agents are combined with anticoagulation using orally given warfarin.

DR. SCHRIER: *Dr. Sasahara, is there any utility in laboratory monitoring of these agents other than for study purposes?*

DR. SASAHARA: I think the importance of laboratory monitoring is to show that you have established a lytic state. This is necessary because of the fixed-dose regimen. You simply want to know that you have a systemic effect, and in appropriate situations in which the clot is fresh, you will get lysis. There is no relationship between the level of fibrinolysis and the frequency of bleeding, the incidence of bleeding or the magnitude of resolution. Because there may be some who have streptococcal antibodies, you will want to do a thrombin time or prothrombin time study to make sure

you have established an effect. With urokinase this is less important because there are essentially no antibodies to this drug.

A PHYSICIAN: Can these drugs be used in an intensive care setting where there may be indwelling lines?

DR. SCHRIER: *This question has come up frequently. Where should these agents be used? Certainly the patients with a massive or submassive pulmonary embolism with hemodynamic problems are going to be in the intensive care unit or coronary care unit. Can these agents be used in the general wards or should patients be transferred to intensive care areas of the hospital?*

DR. SASAHARA: Our patients with pulmonary emboli have all been treated in the intensive care unit. Our patients with venous thrombosis have been treated on the general medical wards. If we have enough nursing help, frequent observations every couple of hours is ideal, but it is feasible to treat patients with deep venous thrombosis on the regular wards with adequate observation. But for pulmonary embolism, transfer the patient to an intensive care unit.

A PHYSICIAN: You made a comment that streptokinase gives a 6 percent allergic reaction and that benadryl and steroids have been used. Can you comment further on the use of these agents?

DR. SASAHARA: The 6 percent reaction rate consisted mainly of hives. Only one patient had transient hypotension, not to shock levels, and a little itching. In two instances administration of the drug was not discontinued and 100 mg of hydrocortisone was given; one of the patients had a transient drop in pressure. In another, 50 to 100 mg of benadryl intravenously took care of the problem. We did not stop administration of the drug.

DR. SCHRIER: *I would like to thank all the participants for the morning.*

Refer to: Wofsy D: Seronegative spondylarthritis—Medical Staff Conference, University of California, San Francisco. West J Med 134:134-140, Feb 1981

Seronegative Spondylarthritis

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR. SMITH:* *In this conference we have asked Dr. David Wofsy from the Division of Rheumatology at the Veterans Administration Medical Center to review the seronegative spondylarthritides and their medical management.*

DR. WOFSY:† Before 1850 little distinction was made between the various forms of chronic arthritis. Even after gout, osteoarthritis and rheumatoid arthritis were clearly separated in the 1850's, most forms of chronic inflammatory polyarthritis remained lumped together as variants of rheumatoid arthritis for another century. In fact, in 1980 it is still true that most patients with ankylosing spondylitis, psoriatic arthritis and the arthritis of chronic inflammatory bowel disease (CIBD) meet the American Rheumatism Association criteria for the diagnosis of rheumatoid arthritis.[1]

In recent years the concept of *rheumatoid variants* has gradually given way to the recognition that entities such as Reiter‡ disease, ankylosing spondylitis, psoriatic arthritis and the arthritis of CIBD are nosologically distinct from rheumatoid arthritis. The seeds for this distinction were sown in the 1940's when it was discovered that many patients with chronic inflammatory polyarthritis had anti-IgG antibodies (rheumatoid factor) in their serum. On this basis, patients with inflammatory polyarthritis could be divided into two main groups, those with rheumatoid factor (seropositive), and those without rheumatoid factor (seronegative). Within the seronegative group, some patients closely resemble those with seropositivity both clinically and radiographically; these people are said to have seronegative rheumatoid arthritis. Other seronegative patients, however, are clinically and radiographically quite different from patients with seropositive rheumatoid arthritis. It is within this group that most patients with ankylosing spondylitis, Reiter disease, psoriatic arthritis, and the arthritis of CIBD are found.

Many of the features that distinguish ankylosing spondylitis, Reiter disease, psoriatic arthritis and the arthritis of CIBD from rheumatoid arthritis tend to associate them with one another. These features include the following: (1) seronegativity, (2) male predominance, (3) common genetic predisposition, reflected in the strong HLA-B27 association, (4) frequent sacroiliac and lower spinal involvement, (5) characteristic radiographic features (periostitis, proliferative erosions), (6) extra-articular manifestations not typical of rheumatoid

*Lloyd H. Smith, Jr, MD, Professor and Chairman, Department of Medicine.

†David Wofsy, MD, Instructor in Medicine, Veterans Administration Medical Center, San Francisco.

‡THE WESTERN JOURNAL's style regarding eponyms is that they are not written in the possessive form; therefore Graves disease, Ewing sarcoma and Paget disease. An explanation may be found on page 78 of the July 1978 issue.

ABBREVIATION USED IN TEXT

CIBD = chronic inflammatory bowel disease

arthritis (uveitis, psoriasiform skin lesions, mucocutaneous ulceration, aortic insufficiency) and (7) absence of extra-articular manifestations typical of rheumatoid arthritis (subcutaneous nodules, pleuropericarditis, Sjögren syndrome, Felty syndrome, vasculitis). On the basis of these similarities, it has become increasingly popular to refer to ankylosing spondylitis, Reiter disease, psoriatic arthritis, and the arthritis of inflammatory bowel disease as "the seronegative spondylarthritides."[2,3] While this designation lacks semantic perfection, it carries with it important clinical, prognostic and therapeutic implications which make up the remainder of our discussion.

Ankylosing Spondylitis

Ankylosing spondylitis[2-5] refers to bilateral sacroiliitis occurring in the absence of psoriasis, inflammatory bowel disease or signs of Reiter disease (Table 1). It is the prototypic seronegative spondarthritis. Axial involvement virtually indistinguishable from ankylosing spondylitis may occur in any of the seronegative spondylarthritides. Like most rheumatic diseases, ankylosing spondylitis has a very broad spectrum of clinical expression. At the severe end of the spectrum are the patients who have inflammation and fusion not only of the sacroiliac joints, but progressing in an ascending fashion throughout the entire vertebral column. This form of the disease has a strong predilection for men (10:1). At the mild end of the spectrum are patients who have sacroiliitis but no spondylitis at all. Calin and Fries[7] recently determined that this form of ankylosing spondylitis is much more common than had been suspected previously. They found that 2 percent of young adult whites have sacroiliitis, and men and women are equally affected. This is a particularly important point since there has been a tendency in the past not to consider the diagnosis of ankylosing spondylitis in women with back pain.

In approximately 50 percent of cases of ankylosing spondylitis, peripheral joints are affected. Indeed, peripheral arthritis may be the presenting feature in as many as 20 percent of cases. Large joints are primarily involved, with hip disease being a particularly important cause of disability.

TABLE 1.—*Clinical Criteria for Ankylosing Spondylitis*[6]

- Persistent low back pain (longer than 3 months) unrelieved by rest
- Limitation of motion in the lumbar spine
- Pain and stiffness in the thoracic region
- Limitation of chest expansion
- Past or present evidence of iritis

Ankylosing spondylitis is confirmed when bilateral sacroiliitis is associated with any *one* of the above clinicial criteria.

Figure 1.—Spur formation with erosion at the calcaneal insertions of the plantar fascia **(below)** and Achilles tendon **(above).**

In addition to inflammation of the joints, there is often inflammation and pain at tendon insertions (enthesopathy). This is a common feature of all the seronegative spondylarthritides. A classic example is heel pain at the insertion of the plantar fascia on the calcaneus (Figure 1).

Ankylosing spondylitis usually begins in young adulthood but often is not recognized until years after the onset of symptoms, by which time severe and irreversible deformity is present. Because much of this deformity can be prevented, early diagnosis is very important. There are several clues to early diagnosis.[8] Back pain which is insidious in onset, occurring in a young adult and persisting for at least three months, is suggestive of sacroiliitis. The pain of sacroiliitis differs from that due to most other causes of low back pain in that it is usually worst in the morning and it generally gets better with exercise. Although sacroiliitis may be accompanied by sciatic radiation, the pain rarely extends below the knee. Iritis is also an important diagnostic clue. It occurs in approximately 25 percent of patients with ankylosing

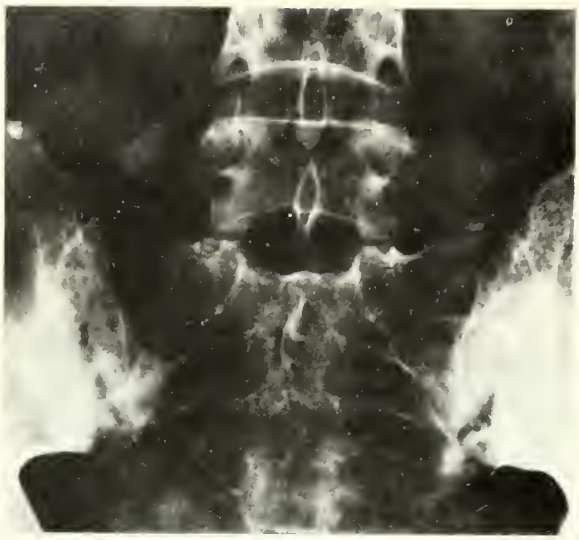


Figure 2.—Bilateral sacroiliitis manifested by subchondral erosions and juxta-articular sclerosis.

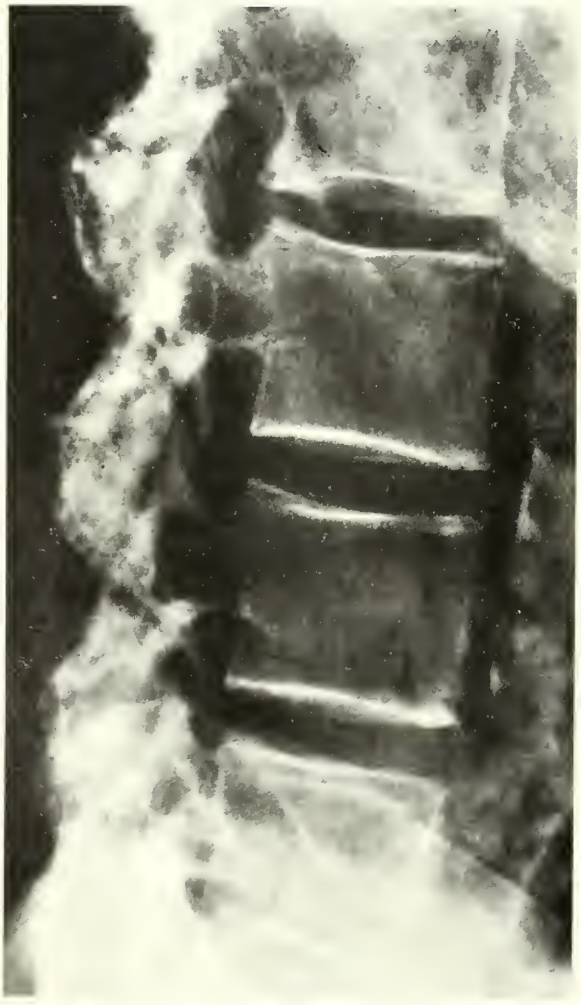


Figure 3.—Vertebral "squaring" in ankylosing spondylitis.

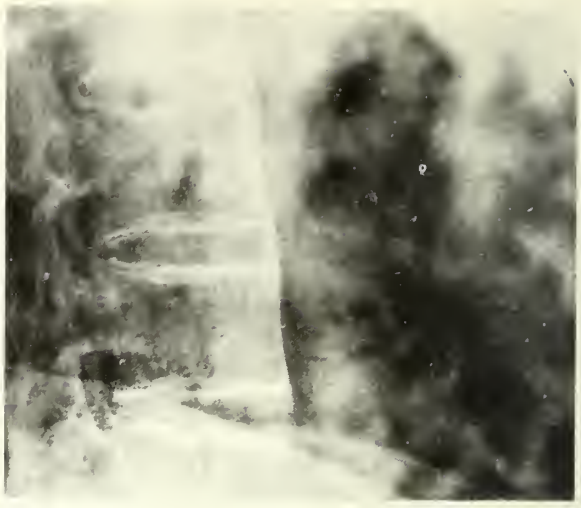


Figure 4.—Anterior calcification of the annulus fibrosis (syndesmophyte formation).

spondylitis. Unexplained iritis in a young person should prompt a search for signs of ankylosing spondylitis.

On physical examination the sacroiliac joints may be tender to palpation or compression. If spondylitis has begun, back motion will be restricted in all directions, as opposed to patients with intervertebral disc disease in whom lateral flexion is usually preserved. Flattening of the back over the lumbar spine is common due to loss of lumbar spinal lordosis and atrophy of paravertebral muscles. In the thoracic region, costovertebral inflammation and fusion lead to decreased chest expansion. This is often present surprisingly early in the course of the disease. Eventually, thoracic and cervical fusion occur and may result in severe kyphotic deformity.

Historical and physical evidence may strongly suggest the diagnosis of ankylosing spondylitis long before roentgenographic evidence is present. However, it is difficult to make the diagnosis with certainty until abnormalities are shown on x-ray studies. The hallmark roentgenographic feature of ankylosing spondylitis is bilateral sacroiliitis. When it involves the axial skeleton, seronegative spondylarthritis is as much a chondritis as it is a synovitis. Inflammation of cartilage in the sacroiliac joints results in irregularity of the joint margins, subchondral erosion and juxta-articular sclerosis (Figure 2). In many cases this process progresses to complete fusion of the sacroiliac joints. In the spine, chondritis involving the vertebral discs affects particularly the outer border of the annulus fibrosis. This causes erosions at the

corners of the vertebrae adjacent to the inflamed annulus fibrosis. As a result, the vertebrae lose their concavity and become relatively square (Figure 3). In addition, secondary ossification of the inflamed outer margin of the annulus fibrosis occurs, creating bony bridges between adjacent vertebral bodies. These intervertebral bridges are called syndesmophytes (Figure 4). Extensive syndesmophyte formation is responsible for the classic radiographic *bamboo spine* appearance (Figure 5).

While x-ray studies play an important role in the evaluation of ankylosing spondylitis, other laboratory tests have limited usefulness. The erythrocyte sedimentation rate is elevated in 80 percent of patients, but it correlates poorly with disease activity. More than 90 percent of whites with ankylosing spondylitis have the HLA-B27 antigen, but so do 8 percent of the general population.[9] Among American blacks with ankylosing spondylitis, only 50 percent have HLA-B27 compared with 2 percent of controls.[9,10] Therefore, because of the frequency of low back pain in the general population, tests for HLA-B27 are rarely helpful clinically. Among white patients, false positive test findings will be common, whereas false negative results will be common among blacks.[11] In many other populations, the frequency of HLA-B27 positivity, and therefore its value as a diagnostic test, has not yet been determined. The HLA-B27 status has no prognostic value in patients with ankylosing spondylitis.[12]

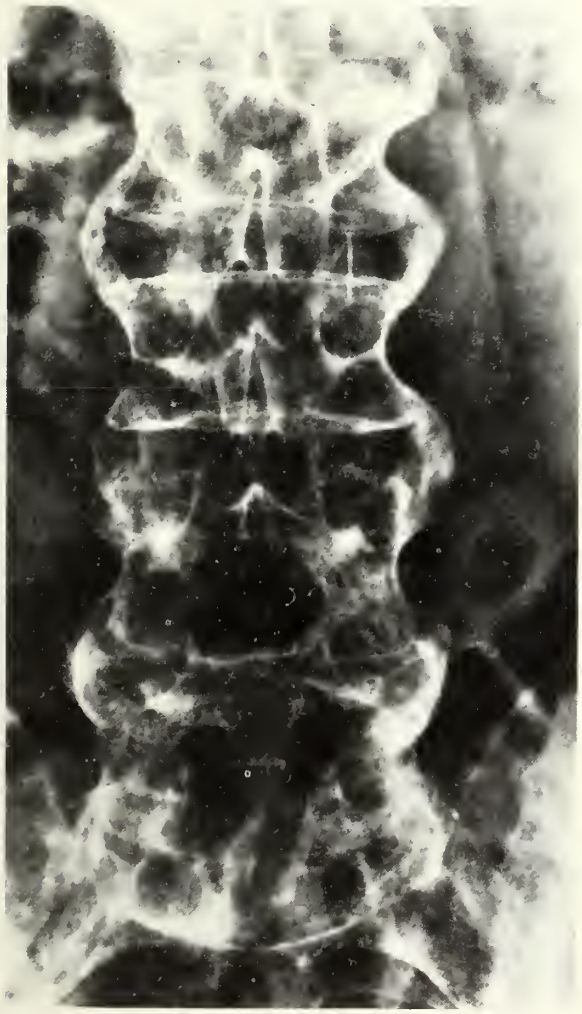


Figure 5.—Bamboo spine, a result of extensive syndesmophyte formation.

The cornerstone of treatment is physical therapy. Since drug therapy does not appear to retard the progression of spinal ankylosis, it is critical that measures be taken which will insure fusion in a position of function rather than in severe kyphosis. In bed, the patient should lie prone, which helps prevent hip flexion contractures, or supine without a pillow. Lying on the side leads to thoracic kyphosis. Out of bed, the patient must constantly work at maintaining an erect posture. This requires strengthening exercises for the back and neck extensor muscles. By comparison, collars and braces are relatively ineffective. Other exercises include deep breathing, to maintain chest expansion, and range of motion exercises, particularly for the hips and shoulders.

Indomethacin and phenylbutazone appear to be superior to aspirin in relieving the pain of ankylosing spondylitis. The comparative efficacy of the newer nonsteroidal anti-inflammatory drugs is unclear. Gold, antimalarial drugs and systemic steroids are not used.

In a minority (5 percent to 10 percent) of patients with ankylosing spondylitis, there will be rapid progression to severe permanent disability. In the remainder, the progression is much more gradual and careful attention to posture and hip motion will prevent severe disability. Anterior uveitis is common in patients with ankylosing spondylitis and may even be the dominant clinical problem. Other clinical problems which infrequently complicate ankylosing spondylitis are aortic insufficiency, apical pulmonary fibrosis, amyloidosis and cauda equina syndrome.

Reiter Disease

Reiter disease is the eponym given to the triad of polyarthritis, urethritis and conjunctivitis. Although these features usually begin at approxi-

mately the same time, each tends to be intermittent and may occur independent of the others. Occasionally, one of the classic features may never appear. In such cases, three additional manifestations peculiar to Reiter disease provide strong suggestive evidence for the diagnosis. These are mucocutaneous ulceration, circinate balanitis and psoriasiform skin lesions on the soles of the feet (keratodermia blenorrhagica).

Reiter disease affects primarily men (10:1), usually beginning during young adulthood. Although some cases are clearly precipitated by antecedent bacterial dysentery, most have no apparent precipitating cause.[2,13] The arthritis of acute Reiter disease is typically an asymmetric, pauciarticular arthritis affecting primarily the large joints of the lower extremities, but any joint may be involved. Like ankylosing spondylitis, Reiter disease is often characterized by an enthesopathy resulting in Achilles tendinitis or plantar fasciitis (or both). In general, the initial attack resolves over several weeks. A minority of patients (20 percent) never have recurrence. The remainder fall into one of the following three groups: (1) recurrent minor symptoms (20 percent), (2) chronic recurrent peripheral arthritis without spondylitis (25 percent) and (3) sacroiliitis with or without spondylitis or peripheral arthritis (35 percent).[14-16]

Laboratory features of Reiter disease are nonspecific. Mild leukocytosis and elevation of the erythrocyte sedimentation rate are common. Analysis of urine may show urethritis or prostatitis. Synovial fluid is inflammatory but has no pathognomonic characteristics. HLA-B27 antigen is present in 75 percent to 80 percent of whites with Reiter disease,[15,16] but this provides relatively little help in the diagnosis of an individual patient. Prognostically, the presence of HLA-B27 increases the likelihood of eventual axial involvement[15] (Table 2). Following an acute attack of Reiter disease, white patients with HLA-B27 have a 60 percent chance of sacroiliitis developing, whereas patients without HLA-B27 have only a 15 percent risk of sacroiliitis. Similar percentages apply to people with psoriatic arthritis[17,18] and chronic inflammatory bowel disease[2] (Table 2). However, it should be emphasized that in each of these diseases, even the patients without HLA-B27 are at significant risk for the development of sacroiliitis. Therefore, all cases must be followed closely for this complication whatever the HLA status of the patients. HLA-B27 positivity has no prognostic value with respect to the other features of Reiter disease.[15]

Radiographically, cortical erosions associated with fluffy periosteal new bone formation are characteristic of peripheral arthritis in the seronegative spondylarthritides (Figure 6). These *proliferative* erosions are quite distinct from the erosions of rheumatoid arthritis, in which there is no periosteal reaction. Periostitis is also common at the calcaneal insertions of the Achilles tendon and plantar fascia (Figure 1), and along the shafts of inflamed phalanges (Figure 7). The sacroiliac and spinal abnormalities in Reiter disease are very similar to those seen in uncomplicated ankylosing spondylitis.

Treatment consists primarily of physical therapy and nonsteroidal anti-inflammatory drugs. Corticosteroids are seldom used. Some have ad-

TABLE 2.—*Risk Factors for Sacroiliitis in Whites*

Population	*Likelihood of Sacroiliitis (Percent)*	
	HLA-B27 Positive	*HLA-B27 Negative*
Reiter disease[15]	60	15
Psoriatic arthritis[17,18]	50	10
Inflammatory bowel disease[2]	50	10
General population[7]	20	<1

Figure 6.—Erosions associated with fluffy periosteal new bone formation, particularly prominent in these fourth and fifth proximal interphalangeal joints, are characteristic of psoriatic arthritis and Reiter disease.

vocated tetracycline for patients with urethritis, but this has no clear effect on the arthritis.[2] The therapeutic approach to patients with axial involvement is identical to that used in ankylosing spondylitis. At present there is no evidence to suggest that any antimalarial drug, gold or penicillamine is effective in Reiter disease.

Psoriatic Arthritis

In approximately 5 percent to 10 percent of people with psoriasis inflammatory polyarthritis develops for which no cause can be found. Infrequently, these patients appear to have coexisting psoriasis and seropositive rheumatoid arthritis. Much more commonly, however, they have a seronegative arthritis which differs significantly from rheumatoid arthritis. It is referred to as psoriatic arthritis.

There are several forms of psoriatic arthritis.[17,18] The most common is asymmetric oligoarticular arthritis, typically involving the interphalangeal joints of the hands and feet, or the large peripheral joints. The classic manifestation of phalangeal involvement is sausage-shaped swelling of a digit, which may be seen not only in psoriatic arthritis but also in Reiter disease. Spondylarthritis, either sacroiliitis alone or in association with spondylitis, accounts for 20 percent of cases of psoriatic arthritis. Symmetrical polyarthritis occurs in an additional 15 percent of cases. It resembles rheumatoid arthritis in distribution, but the rheumatoid factor is absent and the radiographic features are typical of the seronegative spondylarthritides. Finally, a few patients have distal interphalangeal joint involvement only, usually with associated psoriatic nail changes.

Figure 7.—Periosteal reaction in the proximal phalanx of a patient with Reiter disease and sausage-shaped swelling of the middle toe.

Psoriasis usually precedes arthritis although the reverse occasionally occurs. Like ankylosing spondylitis and Reiter disease, psoriatic spondylitis affects primarily men (2:1).[17,18] Unlike ankylosing spondylitis and Reiter disease, however, the other forms of psoriatic arthritis are equally common in men and women.[2,17,18] Similarly, there is a strong association between HLA-B27 and psoriatic spondylitis (60 percent positive in whites), but no such association between HLA-B27 and peripheral psoriatic arthritis.[17,18] Nonetheless, the peripheral forms of psoriatic arthritis closely resemble the other seronegative spondylarthritides both in their asymmetric distribution and their radiographic features. In addition to periostitis and proliferative erosions similar to those seen in Reiter disease, x-rays of the hands may show resorption of the terminal phalangeal tufts (acroosteolysis), joint resorption (arthritis mutilans), or "pencil-in-cup" deformities.

In a minority of patients, the activity of the arthritis parallels the activity of the psoriasis.[19] In these persons treatment which controls the psoriasis may improve the arthritis. For most patients, however, cutaneous and articular manifestations proceed independently and should be treated independently. Nonsteroidal anti-inflammatory drugs are usually effective, and gold has been used successfully in patients with peripheral arthritis.[20] The role of antimalarial drugs in the treatment of psoriatic arthritis is controversial with respect to the drugs' efficacy and toxicity. Penicillamine has not been studied. Although methotrexate has achieved a place in the treatment of psoriasis, it has no role in the treatment of psoriatic arthritis except, perhaps, in a very few persons in whom arthritis clearly parallels the skin disease.

Chronic Inflammatory Bowel Disease

Like Reiter disease and psoriatic arthritis, the arthritis associated with chronic inflammatory

bowel disease may be either peripheral or axial. Approximately 10 percent to 15 percent of people with ulcerative colitis[21] and 5 percent to 10 percent of people with Crohn disease[22] will have peripheral arthritis sometime during the course of their disease. Men and women are equally affected, and there is no HLA-B27 association.[2] The arthritis typically involves the large joints of the lower extremities in an asymmetric oligoarticular fashion. Although arthritis infrequently antedates colitis, it usually coincides with flares of the bowel disease. Attacks of synovitis are generally short and rarely lead to residual deformity or radiographic changes. Treatment consists of aspirin administration, physical therapy and measures directed at controlling the colitis. Indomethacin and phenylbutazone are best avoided in the setting of CIBD. There is little information available concerning the newer nonsteroidal anti-inflammatory drugs.

Sacroiliitis occurs in 15 percent to 20 percent of people with CIBD, and in roughly half of these people spondylitis develops as well.[2,21,22] Men are affected more often than women (2:1), and there is a strong association with HLA-B27 positivity (50 percent to 60 percent in whites).[2] The spondylitis may precede, accompany or follow the onset of CIBD. Its course does not correlate with the course of the colitis, and it has the same prognosis and requires the same treatment as uncomplicated ankylosing spondylitis.

Summary

Ankylosing spondylitis, Reiter disease, psoriatic arthritis and the arthritis of chronic inflammatory bowel disease are closely related diseases referred to as the seronegative spondylarthritides. They are clinically, serologically and radiologically distinct from rheumatoid arthritis. They share many clinical characteristics which are very helpful in diagnosis and which have important implications for prognosis and treatment.

REFERENCES

1. Ropes MW, Bennett EA, Cobb S, et al: 1958 Revision of diagnostic criteria for rheumatoid arthritis. Bull Rheum Dis 9: 175-176, 1958

2. Wright V, Moll JMH: Seronegative Polyarthritis. Amsterdam, Elsevier North Holland Inc., 1976

3. Moll JMH, Haslock I, Macrae IF, et al: Associations between ankylosing spondylitis, psoriatic arthritis, Reiter's disease, the intestinal arthropathies and Bechet's syndrome. Medicine 53: 343-364, 1974

4. Blumberg B, Ragan C: The natural history of rheumatoid spondylitis. Medicine 35:1-31, 1956

5. Calabro JJ, Maltz BA: Current concepts: Ankylosing spondylitis. N Engl J Med 282:606-610, 1970

6. Kellgren JH, Jeffrey MR, Ball J (Eds): The Epidemiology of Chronic Rheumatism, Vol 1. Oxford, Blackwell, 1963, p 326

7. Calin A, Fries JF: Striking prevalence of ankylosing spondylitis in "healthy" W27 positive males and females: A controlled study. N Engl J Med 293:835-839, 1975

8. Calin A, Porta J, Fries JF, et al: Clinical history as a screening test for ankylosing spondylitis. JAMA 237:2613-2614, 1977

9. Schlosstein L, Terasaki PI, Bluestone R, et al: High association of an HL-A antigen, W27, with anklylosing spondylitis. N Engl J Med 288:704-705, 1973

10. Good AE, Kawanishi H, Schultz JS: HLA B27 in blacks with ankylosing spondylitis or Reiter's disease. N Engl J Med 294:166-167, 1976

11. Calin A: HLA B-27: To type or not to type. Ann Intern Med 92:208-211, 1980

12. Khan MA, Kushner I, Braun WE: Comparison of clinical features in HLA-B27 positive and negative patients with ankylosing spondylitis. Arthritis Rheum 20:909-912, 1977

13. Noer HR: An "experimental" epidemic of Reiter's syndrome. JAMA 197:693-698, 1966

14. Sairanen E, Paronen I, Mahonen H: Reiter's syndrome: A follow-up study. Acta Med Scand 185:57-63, 1969

15. Fox R, Calin A, Gerber RC, et al: The chronicity of symptoms and disability in Reiter's syndrome. Ann Intern Med 91:190-193, 1979

16. Butler MJ, Russell AS, Percy JS, et al: A follow-up study of 48 patients with Reiter's syndrome. Am J Med 67:808-810, 1979

17. Kammer FM, Soter NA, Gibson DJ, et al: Psoriatic arthritis: A clinical, immunologic and HLA study of 100 patients. Sem Arthritis Rheum 9:75-97, 1979

18. Lambert JR, Wright V: Psoriatic spondylitis: A clinical and radiological description of the spine in psoriatic arthritis. Quart J Med 46:411-425, 1977

19. Perlman SG, Gerber LH, Roberts RM: Photochemotherapy and psoriatic arthritis: A prospective study. Ann Intern Med 91: 717-722, 1979

20. Dowart BB, Gall EP, Schumacher R, et al: Chrysotherapy in psoriatic arthritis. Arthritis Rheum 21:513-515, 1978

21. Wright V, Watkinson G: The arthritis of ulcerative colitis. Br Med J 2:670-675, 1965

22. Haslock I, Wright V: The musculoskeletal complications of Crohn's disease. Medicine 52:217-225, 1973

Important Advances in Clinical Medicine

Epitomes of Progress — Psychiatry

The Scientific Board of the California Medical Association presents the following inventory of items of progress in psychiatry. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in psychiatry which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Psychiatry of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Meditation: Clinical and Health-Related Applications

REPORTS OF ALTERED STATES of consciousness and extraordinary feats of bodily control by Zen and Yoga masters have been filtering into the West for several decades. However, it is only within the last 15 years that Western scientists and health care professionals have begun to look seriously at Eastern techniques, such as meditation, to determine their possible efficacy in mental and physical health-related concerns.

Meditation refers to a family of techniques that involve a conscious attempt to focus attention in a nonanalytical manner and an effort not to dwell on discursive, ruminating thought. Based on brain neurophysiology, these techniques may be divided into three groups: concentrative meditation, in which the person attempts to focus attention on one particular object (such as a sound, mantra, candle or "third eye"); mindfulness (opening-up) meditation, in which the person attempts to be receptive to whatever internal and external stimuli come into awareness, and a combination of the two, in which the person has an object of focus, but when other stimuli arise, he or she notices the other stimuli and then returns to the original object of focus.

Western research has looked almost exclusively at dependent variables related to meditation as a self-regulation strategy and has been carried out in laboratories and field settings with persons who have been meditating for only a relatively short time. Physiologically, research findings seem convincing that meditation can produce a hypometabolic state in which there is decreased oxygen consumption, reduced heart rate, increased regularity and amplitude of electroencephalographic alpha activity, increased skin resistance and decreased blood pressure.

Because of these physiological changes, it was suggested that meditation would be a useful self-regulation technique for relaxation training. The clinical literature has borne this out. In a recent review of the psychotherapeutic and health-related effects of meditation, it was shown to be a promising clinical intervention in reducing stress and tension, decreasing addictive behaviors and helping to manage hypertension. These clinical changes appear to occur equally well with a variety of different meditation techniques.

Recent research on meditation has attempted to determine more accurately when meditation is an appropriate intervention, and for which persons and for what types of clinical problems it is useful.

It appears that as a self-regulation strategy, meditation is equal to, but no more effective than, other self-control strategies such as biofeedback, hypnosis and progressive relaxation.

DEANE H. SHAPIRO, Jr, PhD

REFERENCES

Benson H: The Relaxation Response. New York, William Morrow, 1975

Otis L: Adverse effects of meditation, *In* Shapiro DH, Walsh RN (Eds): The Science of Meditation. New York, Aldine, 1981 (In press)

Shapiro DH: Meditation: Self-Regulation Strategy and Altered State of Consciousness. New York, Aldine, 1980

Shapiro DH: A clinical and physiological comparison of meditation with other self-control strategies: Biofeedback, hypnosis, progressive relaxation. Am J Psychiatry, 1981 (In press)

Shapiro DH Jr, Giber D: Meditation and psychotherapeutic effects—Self-regulation strategy and altered state of consciousness. Arch Gen Psychiatry 35:294-302, Mar 1978

Schwartz GE, Davidson RJ, Goleman DJ: Patterning of cognitive and somatic processes in the self-regulation of anxiety: Effects of meditation versus exercise. Psychosom Med 40:321-328, Jun 1978

The Diagnosis of Schizophrenia

THE ADOPTION BY THE American Psychiatric Association of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III, effective 1980) entails many changes in the diagnostic practices of American psychiatrists and other mental health professionals. An important inclusion in DSM-III is a particular set of diagnostic criteria for schizophrenia. These criteria render a clear verdict regarding a critical dispute that has lasted almost a century over opposing concepts of this most distressing and disabling of mental disorders.

Eugen Bleuler, who formulated the term schizophrenia, based his concept of the disorder on certain essential symptoms that could be identified in many persons who had never been psychotically ill. He believed that in mild grades and in its simple form, schizophrenia was extremely widespread in nonclinical populations:

> . . . the simple schizophrenics vegetate as day laborers, peddlers, even as servants. They are also vagabonds and hoboes. . . . On the higher levels of society, the most common type is the wife. . . , who is unbearable, constantly scolding, nagging, always making demands, but never recognizing duties.

Bleuler's broad concept of schizophrenia became rooted in American psychiatric diagnostic practice as exemplified by the very general diagnostic criteria established for schizophrenia in DSM-I (1952) and which persisted in DSM-II (1968). Many clinicians came to share the dismay of sociologically oriented observers that the label of schizophrenia, admittedly a sticky one, was being applied too often in a haphazard and potentially damaging way to patients (and nonpatients) with extraordinarily varied presentations in diverse settings and under diverse conditions of evaluation.

DSM-III stipulates that for a diagnosis of schizophrenia to be made, a patient must have had signs of the illness continuously for at least six months and that the six-month period must include an active phase with clearly psychotic symptoms (from an explicit list). Although DSM-III includes a list of potential prodromal or residual symptoms of schizophrenia, which encompasses Bleuler's essential symptoms, these are neither necessary nor sufficient for a diagnosis of schizophrenia.

The definitional requirement that schizophrenia be an illness characterized by psychotic symptoms and a continuous course of at least six months duration may help reduce the still existing skepticism that there is such a group of mental disorders and may improve treatment and research efforts for those who suffer from them. American psychiatry has taken a large step toward the Scandinavian practice of waiting five years from the onset of initial symptoms before confirming a diagnosis of schizophrenia.

MARVIN KARNO, MD

REFERENCES

Bleuler E: Dementia Praecox or the Group of Schizophenias. New York, International Universities Press, 1950

Diagnostic and Statistical Manual of Mental Disorders, 3rd Ed. Washington, DC, American Psychiatric Association, 1980

Tardive Dyskinesia

TARDIVE DYSKINESIA IS the most serious long-term side effect of all antipsychotic drugs. These drugs, in use for some 25 years, are the cornerstone of therapy in schizophrenia. Aftercare studies show substantial drug-placebo differences in relapse rates (favoring antipsychotic drugs) and, accordingly, it is accepted practice to prescribe maintenance antipsychotic drugs to most schizophrenic patients after their discharge.

Tardive dyskinesia consists of repetitive, involuntary movements that primarily involve, at least initially, the muscles of the face, lips and tongue. Involuntary mouthing, chewing, sucking, licking movements and tongue movements inside the mouth are frequent early manifestations. Later, the syndrome may include grotesque facial grimaces. choreoathetoid-type movements of the fingers, hands, arms and feet, abnormal trunk movements, peculiar gaits and abnormal diaphragmatic movements that result in grunting, difficult respiration and voice abnormalities.

Tardive dyskinesia occurs after several years (occasionally months) of antipsychotic drug therapy, with an estimated prevalence of between 15 percent and 50 percent after long-term therapy.

Patients are usually unaware of any abnormal

movements; thus, detection is entirely up to their physicians. If detected early, the dyskinesia will usually fade away if antipsychotic drugs are stopped; if drugs are continued, however, the dyskinesia is likely to become irreversible and may grow progressively worse.

Because there is no satisfactory treatment for tardive dyskinesia, we must try to prevent it. Much can be done by reducing drug exposure. Some, particularly those with misdiagnosed manic-depressive and panic disorders, are best managed with lithium carbonate and imipramine (Tofranil), respectively. Many cases of chronic schizophrenia can be maintained on much lower maintenance doses—doses as low as 1 mg of haloperidol (Haldol) or 50 mg of thioridazine (Mellaril) may suffice. Other patients, particularly those with families who can watch for the earliest signs of relapse, can be managed with intermittent drug treatment.

THEODORE VAN PUTTEN, MD

REFERENCES

Gardos G, Cole JO: Overview: Public health issues in tardive dyskinesia. Am J Psychiatry 137:776-781, Jul 1980

Klawans HL, Goetz CG, Perlik S: Tardive dyskinesia: Review and update. Am J Psychiatry 137:900-908, Aug 1980

Davis JM: Overview: Maintenance therapy in psychiatry: I. Schizophrenia. Am J Psychiatry 132:1237-1245, Dec 1975

Screening for Endogenous Depression: The Dexamethasone Suppression Test

A MAJOR GOAL of research in biological psychiatry has been to identify possible state and trait markers of psychiatric illness that might better predict drug response and prognosis than predictions based on clinical observation alone.

Although a variety of neuroendocrine and biochemical abnormalities have been reported for differing groups of psychiatric patients, most of these findings either have been difficult to replicate or have lacked clinical usefulness because of the complexity of the procedure involved, the expense of the test or the possibility of interference by psychotherapeutic medication. Also, in some instances, large statistical variances have made individual data equivocal. The first screening test to overcome these obstacles successfully has been the dexamethasone suppression test (DST), a test commonly used in the diagnosis of Cushing syndrome, but modified somewhat for usage with psychiatric patients. Current practice calls for the administration of 1 mg of dexamethasone at 11:30 PM and plasma samples assayed for cortisol at 8:00 AM on the day of administration and at 8:00 AM, 4:00 PM and 11:00 PM on the day after dexamethasone has been given. Approximately 50 percent to 60 percent of depressed patients show either a failure to suppress plasma cortisol levels with dexamethasone or an early escape from suppression (defined as 5 mg per dl or greater at any sampling point after administration of the drug). The principal usefulness of a positive finding at present is in assisting a clinician to make a differential diagnosis by helping to identify patients most likely to respond to antidepressant drugs. Drug-responsive depressions are thought to be more often endogenous as opposed to neurotic or characterological.

The DST also appears to help in the prediction of a beneficial response to lithium in catatonic patients and in the separation of primary from secondary forms of depression. Because the neuroendocrine abnormality appears to be state-specific (that is, patients usually show a normal response to dexamethasone with the resolution of their depression), serial DST's have been advocated as a possible indicator of how long to treat a patient with tricyclic agents.

VICTOR I. REUS, MD

REFERENCES

Brown WA, Johnston R, Mayfield D: The 24-hour dexamethasone suppression test in a clinical setting: Relationship to diagnosis, symptoms, and response to treatment. Am J Psychiatry 136:543-547, Apr 1979

Carroll BJ, Curtis GC, Mendels J: Neuroendocrine regulation in depression: I. Limbic system-adrenocortical dysfunction. Arch Gen Psychiatry 33:1039-1044, Sep 1976

Ettigi PG, Brown GM: Psychoneuroendocrinology of affective disorder: An overview. Am J Psychiatry 134:493-501, May 1977

Pseudodementia Syndrome

IN THE PSEUDODEMENTIA SYNDROME signs and symptoms that are consistent with irreversible organic brain disorders are predominant. However, in fact, these represent manifestations of nonorganic psychopathology, occurring typically as a major depressive episode. Failure to consider reversible causes of apparent dementing illness in the differential diagnosis of such patients can result in inappropriate treatment as well as an overdiagnosis of dementia. The pseudodementia syndrome often occurs in those age groups in which presenile and senile dementias are more prevalent, leading to further inaccuracies of diagnosis based on the notion that organic brain syndromes are a natural or expected concomitant of aging; however, this has not been shown to be the case.

The index of suspicion for pseudodementia is raised by several clinical features that help to differentiate the syndrome from true dementia. Among these are the following: progression of

symptoms after onset is rapid; medical attention tends to be sought shortly after onset of such symptoms and, frequently, a previous history of psychiatric disturbance exists. Patients tend not to conceal but to emphasize their disability, and there is often early and prominent loss of social skills. Preservation of attention and concentration is common, disturbance in remote memory is often as severe as that for recent memory and patients tend to give "don't know" answers rather than near-miss responses.

It is important to rule out treatable metabolic or structural disease through careful physical examination and ancillary studies such as computed cerebral tomography. However, because enlarged cortical sulci and ventricular dilatation on computed tomographic (CT) scans do not necessarily imply the existence of dementing illness, the recognition of pseudodementia in the presence of cerebral atrophy must be made on clinical grounds. In this process, psychometric evaluation, including neuropsychological assessment, may be invaluable. Equally important, an accurate psychiatric diagnosis must be established to effect appropriate treatment interventions.

EDWARD H. LISTON, MD

REFERENCES

Wells CE: Pseudodementia. Am J Psychiatry 136:895-900, Jul 1979

Jarvik LF, Ruth V, Matsuyama SS: Organic brain syndrome and aging—A six-year follow-up of surviving twins. Arch Gen Psychiatry 37:280-286, Mar 1980

Besdine RW, Brody JA, Butler RN, et al: Senility reconsidered: Treatment possibilities for mental impairment in the elderly. JAMA 244:259-263, Jul 18, 1980

The Therapeutic Alliance and the Outcome of Psychotherapy

THE IMPORTANCE OF establishing and maintaining a therapeutic alliance in psychotherapy has been a subject of intense clinical interest since Freud's early attempts to define the treatment relationship. The therapeutic alliance has meant an attitude of positive regard between a patient and therapist, the patient's experience of the therapist as supportive and helpful and a sense that the patient and therapist are working together to restore the patient's well-being. There is an agreement between them concerning the techniques and objectives of their collaboration.

The contribution of such a cooperative relationship to the success of psychotherapy is an accepted clinical dictum in diverse psychotherapeutic schools. What is novel, however, is a recent convergence of evidence among psychotherapy researchers to support this clinical lore. At the 1980 Society for Psychotherapy Research meetings in Asilomar, California, five research centers working independently in the United States and Canada reported carefully instituted and reliably rated use of the Therapeutic Alliance Scales. In each instance raters, who had no knowledge of the treatment outcomes, scored audiotapes or transcripts of selected early and late psychotherapy sessions. The ratings were predictive of outcome; a positive alliance was associated with success in psychotherapy and a poor alliance was related to persistent symptomatic distress and social functioning disturbances. In one study, the patient's contribution to the alliance was decisive. Further, ratings of early treatment hours were predictive of outcome, suggesting that by the third to fifth session an attitudinal-affective climate had been created in the therapist-patient relationship that was relatively stable and was a useful prognostic indicator.

These studies have implications for both the practice and evaluation of psychotherapy because they show agreement between hypothesis-generating, descriptive clinical reports and hypothesis-testing research studies. This research is being followed with interest by clinicians who, historically, have ignored scientific evaluations of psychotherapy as esoteric, irrelevant or incomprehensible in relation to the real-life dilemmas of treating patients. Additionally, because the quality of the therapeutic alliance established early in treatment is predictive of the outcome, cases could be monitored while therapy is in progress, thereby permitting therapists to introduce new strategies to counter negative trends and avert treatment failures.

CHARLES MARMAR, MD

REFERENCES

Greenson RR: The working alliance and the transference neurosis. Psychoanal Q 34:155-181, Apr 1965

Luborsky L: Helping alliances in psychotherapy, *In* Claghorn JL (Ed): Successful Psychotherapy: Proceedings of the 9th Annual Symposium, November 19-21, 1975, Texas Research Institute of Mental Sciences. New York, Brunner/Mazel, 1976

Marziali E, Marmar C, Krupnick J: Therapeutic alliance scales: Their development and relationship to psychotherapy outcome. Am J Psychiatry, 1981 (In press)

Gomes-Schwartz B: Effective ingredients in psychotherapy: Prediction of outcome from process variables. J Consult Clin Psychol 46:1023-1035, Oct 1978

Cholinergic Hypersensitivity in Patients With Affective Disorders

CONSIDERABLE EVIDENCE INDICATES that depression may reflect increased central acetylcholine activity, relative to catecholaminergic or serotonergic activity, and that mania may be due to the converse mechanism. Most antidepressant drugs have anticholinergic or acetylcholine-sup-

pressant properties, and those drugs which can induce depression, such as reserpine, generally increase cholinergic activity. Supporting the possibility that acetylcholine is involved in the regulation of affect are observations that physostigmine, a centrally acting cholinesterase inhibitor that increases brain acetylcholine, (1) causes a rapid and dramatic antagonism of manic symptoms, as well as anergy and mild depression in patients with bipolar affective disorders, (2) antagonizes methylphenidate-induced euphoria and psychostimulation and (3) causes a severe depressed mood in marijuana-intoxicated normal subjects. Similarly, choline, an acetylcholine precursor, can cause increases in depression in patients with tardive dyskinesia.

In addition, evidence exists that patients with affective disorders may be relatively more sensitive than normal persons and patients with nonaffective disorders to such cholinergic agents as physostigmine and arecholine. While most people become anergic after receiving physostigmine, in normal volunteers a depressed mood develops infrequently after receiving physostigmine. However, depression often develops in patients with an affective component of their illness, such as manic, depressive and schizoaffective conditions, and in euthymic patients with a history of affective disorders after they have received physostigmine. Similarly, deanol, a presumed acetylcholine precursor, has been found to cause selectively the development of affective symptoms in patients with tardive dyskinesia who have had a past history of an affective disorder. Also, patients with affective disorders appear to be relatively more reactive to the anergic, inhibitory, negative-mood-inducing and emetic effects of physostigmine. Furthermore, rapid eye movement (REM) latency, an acetylcholine-sensitive sleep determination that measures the time from onset of sleep until onset of the first REM period, is more sensitive to being decreased by cholinergic agents in patients with affective disorders than in normal subjects.

Thus, acetylcholine may be involved directly or indirectly in the regulation of affect, and patients with affective disorders appear to be more sensitive to the effects of cholinomimetic drugs.

DAVID S. JANOWSKY, MD

REFERENCES

Janowsky DS, el-Yousef MK, Davis JM, et al: A cholinergic-adrenergic hypothesis of mania and depression. Lancet 1:632-635, Sep 23, 1972

Janowsky DS, el-Yousef MK, Davis JM: Acetylcholine and depression. Psychosom Med 36:248, May-Jun 1974

Davis KL, Berger PA, Hollister LE, et al: Physostigmine in mania. Arch Gen Psychiatry 35:119-122, Jan 1978

Sitaram N, Nurnberger JI, Gershon ES, et al: Faster cholinergic REM sleep induction in euthymic patients with primary affective illness. Science 208:200-202, Apr 11, 1980

Cognitive and Behavioral Psychotherapeutic Approaches to Depression

BEHAVIORAL AND COGNITIVE-BEHAVIORAL forms of treatment for nonbipolar, nonpsychotic outpatients suffering from depression focus on teaching them specific skills in a structured, time-limited context (usually in 12 to 20 sessions). Patients are given a rationale that describes the relationship between mood and behavioral or cognitive patterns; they are taught methods to alter these patterns in a manner that will decrease the probability of debilitating depression; they are instructed to practice their newly acquired skills outside the therapy sessions and they are encouraged to attribute the therapeutic change to their continued use of these skills in their everyday life. The theoretical effect of these techniques is to increase a patient's feelings of self-efficacy, to reduce feelings of hopelessness and helplessness and to avoid creating continued dependence on the therapist.

The directive nature of these therapies has lent itself to the development of manuals and texts that describe the treatment techniques in great detail. Beck and his colleagues at the University of Pennsylvania have developed and tested a cognitive-behavior therapy manual, which is now being evaluated in a major National Institute of Mental Health (NIMH) collaborative treatment outcome study. An earlier study has suggested that Beck's approach may be more effective than use of imipramine alone because of its lower treatment dropout rate and greater reduction in depression level. Patients' pessimistic assumptions and beliefs, the dysfunctional way they construe their world, and such logical distortions as overgeneralization, mislabeling and arbitrary inferences are identified and altered. At the same time, homework that focuses on daily behavior is used to facilitate improvement.

Lewinsohn and colleagues at the University of Oregon have developed a more behavior-oriented approach. Patients keep daily records of their pleasant activities and interpersonal contacts and their thoughts. They are taught to identify those activities or thoughts (or both) that most affect their mood and are then trained to alter them using social learning self-control methods. Patients

who continue to use these methods after therapy has ended have reported further alleviation in levels of depression than they had experienced by the end of the formal treatment program.

RICARDO F. MUÑOZ, PhD

REFERENCES

Beck AT, Rush AJ, Shaw BF, et al: Cognitive Therapy of Depression. New York, Guilford Press, 1979

Lewinsohn PM, Muñoz RF, Youngren MA, et al: Control Your Depression. Englewood Cliffs, NJ, Prentice-Hall, 1978

Rush AJ, Beck AT, Kovacs M, et al: Comparative efficacy of cognitive therapy and pharmacotherapy in the treatment of depressed outpatients. Cognitive Therapy and Research 1:17-37, Jan 1977

Zeiss AM, Lewinsohn PM, Muñoz RF: Nonspecific improvement effects in depression using interpersonal skills training, pleasant activity schedules, or cognitive training. J Consult Clin Psychol 47:427-439, Jun 1979

Hyperkinetic Behavior Disorder

HYPERKINETIC BEHAVIOR (minimal brain dysfunction, attentional deficit disorder) is a common disorder that afflicts 1 out of 20 school-age children. Many disorders of childhood are transient and do not predict psychopathologic conditions that develop later in life. However, recent studies have found that this is clearly not the case for this disorder. As these children grow older, although some types of behavior (such as restlessness and gross motor activity) become less prominent, new and more serious problems frequently arise. By their midteens, most of these children have problems of academic failure (despite normal intelligence). One out of four are found to have severe antisocial behavior, with 20 percent of these cases resulting in court referral. When this disorder persists into adulthood, the psychopathology may include alcoholism, sociopathy and, possibly, psychosis.

Therapy most often consists of single-treatment approaches such as stimulant medication, the Feingold diet, educational intervention, psychotherapy and behavior modification. Stimulant medication without question results in short-term improvements in behavior in about 70 percent of these children; however, the Feingold diet is probably beneficial in no more than 5 percent. Unfortunately, none of the above treatments has been found to produce long-term benefits, such as improved scholastic performance, better social adjustment or a reduction in antisocial behavior.

The discouraging lack of long-term beneficial effects from the single-treatment approach has resulted in studies of combined treatment for this disorder. Such treatment is based on the premise that most of these children are multihandicapped. Hence, it does not make good clinical sense to attempt to treat one disability while ignoring others. Such treatment may point the way to the future. In a three-year study of hyperactive boys, it was found that multimodality treatment resulted in academic gains, better social adjustment at home and at school and a reduction of antisocial behavior. Further studies will be needed to ascertain whether this improvement will persist into adulthood.

JAMES H. SATTERFIELD, MD

REFERENCES

Satterfield JH, Cantwell DP, Satterfield BT: Multimodality treatment: A one-year follow-up of 84 hyperactive boys. Arch Gen Psychiatry 36:965-974, Aug 1979

Wood DR, Reimherr FW, Wender PH, et al: Diagnosis and treatment of minimal brain dysfunction in adults: A preliminary report. Arch Gen Psychiatry 33:1453-1460, Dec 1976

Satterfield JH, Satterfield BT, Cantwell DP: Multimodality treatment: A two-year evaluation of 61 hyperactive boys. Arch Gen Psychiatry 37:915-919, Aug 1980

Satterfield JH, Satterfield BT, Cantwell DP: Three-year multimodality treatment and study of hyperactive boys. Pediatrics, 1981 (In press)

ADVISORY PANEL TO THE SECTION ON PSYCHIATRY

ENOCH CALLAWAY, MD
Advisory Panel Chairman
Section Editor
CMA Scientific Board Representative
San Francisco

ROBERT KLAMT, MD
CMA Section Chairman
Modesto

ELAINE KNUTSEN, MD
CMA Section Secretary
Imola

THOMAS E. PRESTON, MD
CMA Section Assistant Secretary
Beverly Hills

BENJAMIN KOVITZ, MD
Loma Linda University

THOMAS A. GONDA, MD
Stanford University

JOE TUPIN, MD
University of California, Davis

LAWRENCE D. SPORTY, MD
University of California, Irvine

LOUIS J. WEST, MD
University of California, Los Angeles

LEWIS JUDD, MD
University of California, San Diego

ROBERT WALLERSTEIN, MD
University of California, San Francisco

R. BRUCE SLOAN, MD
University of Southern California
Los Angeles

J. BRAND BRICKMAN, MD
La Jolla

JAMES MARGOLIS, MD
Carmichael

DAVID MARKEL, MD
Los Angeles

DAVID OLENIK, MD
La Jolla

EDITORIALS

Hopes and No Hopes for the Next Quadrennium

IN THIS EDITORIAL the next quadrennium refers to the next four years during which the incoming national administration will be in office. It is possible, even likely, that there will be some changes in national policy, but the roots of much that is in place extend well into the fabric of the past and have, for better or worse, now extended well into the fabric of the present. Thus, for medicine and health care there can be hope for some things and no hope for others in the next quadrennium.

One can hope, for example, that there will be enough relaxation in some of the more stifling government regulations regarding health and health care so that costs engendered by them can be somewhat reduced, and also so that America will be able to reaffirm its position of primacy in world medicine. Great as may be the need to curtail federal spending, one can hope that worthwhile programs in the health field will not be summarily closed off with no real consideration of the investment in them or of the potential for a reasonable return on the investment. One can hope that there will be some tangible reaffirmation of the importance of quality in patient care and some reversal of recent trends which tend to foster professional mediocrity, or worse, under one or another social, economic or political theory. And one can hope for some separation of care of the sick from the fostering of health, well-being and quality of life on the one hand, and welfare support for the aged, infirm and the handicapped on the other, while at the same time recognizing the important relationships of medicine with each of these.

There can be no hope that the next quadrennium will see any significant return to *the good old days* as some would wish. Increasing interdependence is a fact of life and now the challenge is to accommodate to this without significant loss of freedom and independence. The hope is that this can somehow be done, but the experience to date suggests that more laws and regulations further restricting freedom and independence do not seem to be the way. Also, there is no hope that government caps or ceilings can accomplish cost containment in health care without what amounts to rationing of services by whatever name this may be called. And it is unlikely that the next quadrennium will see any significant change in the intrinsic power and constancy of the well-established federal, state and local health care bureaucracies.

It is regrettable but true that elected officials in America, whether in the public or private sector, tend to think only from one election to the next, which means that the effective attention span for any problem is usually only two to four years. Unfortunately the problems of health and health care are seldom understood, not to mention solved, within this short time frame. In fairness, within government the uniformed United States Public Health Service (USPHS) is a permanent agency that tries to take a longer look at the problems of health and health care. However, the USPHS is at a disadvantage in that it is outside the system and therefore only partially understands it, and thus is only able to influence it through laws and regulations imposed upon it from outside. What is greatly needed is a problem-solving mechanism for health care outside of government,

one that functions effectively within the health care system as part of it, and one that is able to develop a consensus mode of collaboration among the free, independent and autonomous organizations, institutions and agencies which make up the system.

One is free to speculate whether there is hope or no hope that such a mechanism can or will come into being during the next quadrennium, and if it does, whether there is hope or no hope that it can be made to work any better than what we now have.

—MSMW

Platelets in Perspective

BLOOD PLATELETS have at last developed personalities, and multifaceted ones at that. Perhaps it is not surprising it took so long. Platelets were the last of the formed elements in circulating blood to be recognized. As late as 1932 it was still uncertain whether platelets represented a distinct population derived from bone marrow precursors or were pinched off fragments of lymphocyte cytoplasm.[1] In 1976 the suggestion that platelets were products of erythrocytes could still be given serious consideration.[2] Even the principal function of platelets was not understood for nearly a century. Early investigators clearly recognized the involvement of platelets at sites of vascular injury, but excitement generated by discoveries in the field of blood coagulation dominated the subject of hemostasis until recent years. Small wonder that the complex nature and importance of blood platelets was not appreciated until the present decade.

Elsewhere in this issue Huebsch and Harker cogently present the dramatic changes that have occurred in our understanding of platelets. In a succinct review of physiology, the authors point out the remarkable variability in the response of platelets to hemostatic stimuli. While platelets can be activated independently by thrombin, collagen, adenosine diphosphate, epinephrine or thromboxane A_2, in general these factors act synergistically to promote accumulation of additional platelets to already adherent cells at sites of vascular damage. Although evolutionary processes resulted in development of only a single type of circulating cell responsible for maintaining vascular integrity, the platelet has been endowed with numerous mechanisms for achieving the exercise of its hemostatic function.[3] This versatility may explain why it has been difficult to block the platelet contribution to thrombotic disease by selection of drugs which influence only one or two of its mechanisms.[4] The action of thrombin on platelets is not blocked by aspirin, as noted by the authors of this review, and platelets treated with aspirin in vivo can be made sensitive to all aggregating agents by brief exposure to physiological concentrations of epinephrine.[5] Thus, efforts to pharmacologically modify platelets must take into account the remarkable ability of these cells to use alternate mechanisms to secure hemostasis.

Authors of this review have provided an excellent new classification of platelet functional deficiencies. Disorders of substrate connective tissue have been placed at the head of the list, and this position of primacy is appropriate. Interaction between platelets and the vessel wall has received increasing attention, and the importance of connective tissue elements in the hemostatic response is now well established. Therefore, it is not surprising to see Ehlers-Danlos syndrome, scurvy and amyloidosis listed under disorders of platelet function, nor is it strange to find uremia listed under disorders of platelet adhesion. Toxic by-products generated during the uremic state were believed to be the cause of abnormal platelet function,[6] but more recent studies have suggested that blood vessels in patients with uremia produce excessive amounts of prostacyclin (PGI_2).[7] PGI_2 is the major metabolite derived from arachidonic acid during prostaglandin synthesis by vascular endothelium and smooth muscle cells, and one of the most powerful natural inhibitors of platelet function. It has been proposed that an imbalance in the synthesis of thromboxanes by platelets and PGI_2 by blood vessels may contribute to thrombosis or hemorrhagic disease.[8] Therefore, excessive formation of PGI_2 and suppression of platelet function may be as important as toxic metabolites of urea in causing the bleeding problems of patients with uremia.

While an imbalance in PGI_2 may contribute to hemorrhagic problems of patients with uremia, it is becoming apparent that the use of this compound or its stable analogues may reverse or ameliorate vaso-occlusive disease. Space did not permit Drs. Huebsch and Harker to explore this new area of management for patients with platelet-related vascular disease. However, we are on the

threshold of a new era in the management of acute and chronic blood vessel and platelet disorders, and the fine review by Huebsch and Harker places the explosion of new knowledge into a perspective that can be understood and used effectively by physicians involved in the diagnosis and care of such patients.

JAMES G. WHITE, MD
Professor of Pediatrics,
Laboratory Medicine and Pathology
University of Minnesota Medical School
Minneapolis

REFERENCES

1. Tocantins LM: The blood platelets—Past, present and future, In Johnson SA, Monto RW, Rebuck JW, et al (Eds): Blood Platelets. Boston, Little, Brown and Co, 1961, pp 3-6

2. Leiter SS: The human blood platelet: Its derivation from the red blood cells—A morphologic study. Folia Haematol (Leipz) 103: 878-882, 1976 (Eng Abstr)

3. White JG, Gerrard JM: The cell biology of platelets, *In* Glynn WE, Hauck JC, Weissmann G (Eds): Handbook of Inflammation—II: The Cell Biology of Inflammation. New York, Elsevier/North Holland, Biomedical Press 1980, pp 81-143

4. Schoenberger JA: A randomized, controlled trial of aspirin in persons recovered from myocardial infarction. JAMA 243:661-669, Feb 15, 1980

5. Rao GHR, Johnson GJ, White JG: Influence of epinephrine on the aggregation response of aspirin-treated platelets. Prostaglandins and Medicine 5:45-58, 1980

6. Rabiner SF: Uremic bleeding, *In* Spaet TH (Ed): Progress in Hemostasis and Thrombosis, Vol 1. New York, Grune and Stratton, 1972, p 233

7. Remuzzi G, Cavenaghi AE, Mecca G, et al: Prostacyclin (PGI_2) and bleeding time in uremic patients (Letter). Throm Res 11:919-920, Dec 1977

8. Gerrard JM, White JG: Prostaglandins and thromboxanes: 'Middlemen' modulating platelet function in hemostasis and thrombosis, *In* Spaet TH (Ed): Progress in Hemostasis and Thrombosis, Vol 4. New York, Grune and Stratton, 1978, p 87

Has the Public's Interest in Health Care Peaked?

THE PUBLIC'S INTEREST in health care developed as a result of the remarkable advances in medical knowledge that occurred during and after World War II. The flame of this interest was fanned by many less than responsible promises of imminent cures for cancer and many other diseases, and by a forced draft of the flame from the federal government, which promoted health care as a right and something to be best achieved by nationalization. Somehow it was assumed that if there was enough health care around, and if everyone had all they needed or wanted of it, then everyone would be healthy. Unfortunately, as more and better (and also more expensive) health care became more available to more people, the dream did not come true. There is a suspicion, moreover, that the rate of improvement in the nation's health may not be keeping up with the rate of increase in the cost of all this health care.

Is it possible that the public's interest in health care may have peaked? At least at the federal level there is considerable evidence that this may be the case. Funding for medical research has not kept pace with inflation, support for the education and training of doctors and nurses has been reduced, and there is serious talk of arbitrary caps on patient care services to control their rising costs. One is even hearing less talk of the right to health care. Curiously, while all this is happening, there is a growing interest in health itself among individual persons—admittedly with some encouragement by government. Concern with nutrition and personal physical fitness and attention to disease prevention are clearly evident everywhere. In a sense this personal involvement seems to be replacing what was often almost an obsession with health care as a goal for society.

So it seems there may be good reason to believe that monetary inflation, energy shortages, and a likely competitive weakness in both the national economy and the national defense are making health care a lower priority in the public's view. If this is so, then one may expect fewer dollars for health care, whether from private or public sources. Also, possibly there may be less interference by government in patient care, and perhaps greater opportunities for innovation and improvement—the latter a consummation devoutly to be wished by physicians.

—MSMW

Why Thrombolytic Therapy

THROMBOLYTIC THERAPY has now become established as a therapeutic measure in this country; several thousand cases have been treated since streptokinase and urokinase were licensed and the number of patients receiving these drugs and the number of physicians employing them has been rising rapidly in recent months. This development and the conclusion of a recently held National Institutes of Health Consensus Development Conference,[1] which encourages physicians to use thrombolytic therapy for the treatment of acute deep vein thrombosis and pulmonary embolism, has spurred renewed and increasing interest

A Specialty Conference entitled "The Use of Fibrinolytic Agents" appears elsewhere in this issue.

in this subject. The purpose of this editorial is to provide the rationale for the conference statement "When properly used in tandem with anticoagulation, thrombolytic therapy as currently practiced, represents a significant advance in the management of proximal acute deep vein thrombosis and the more severe forms of pulmonary embolism."[1] This statement was based on two major considerations: better clarification and reduction of the bleeding risk associated with this form of therapy, and a more extensive documentation of the clinical benefits to be achieved.

Better Clarification and Reduction of the Bleeding Risk

While bleeding is the major complication of thrombolytic therapy and occurs more frequently than with conventional anticoagulants, this increased frequency is almost exclusively due to superficial or surface bleeding at the site of invasive procedures. As such, it represents an integral part of the therapy since these agents promote the lysis of fibrin in hemostatic plugs, just as they do in dissolving thrombi or emboli. The high bleeding rate previously described for both lytic therapy (45 percent) and for heparin therapy (27 percent) in the National Institutes of Health sponsored controlled trials in pulmonary embolism[2,3] and which tempered enthusiasm for the use of urokinase and streptokinase was shown to be directly traceable to and occurred at the immediate site of the multiple invasive procedures required to obtain the data as directed by the aggressive protocol.[2,3] In current practice this type of bleeding has been sharply reduced and controlled by careful patient selection, avoidance of nonessential invasive and diagnostic procedures and improved management[4,5]; with proper attention to details, it no longer represents a major problem.

As for internal bleeding, its incidence is similar to that observed with conventional anticoagulation—that is, approximately 5 percent.[6] However, a continuing major concern with lytic therapy as compared with heparin is the somewhat higher incidence of cerebral hemorrhage (1 percent for lytic therapy as compared with 0.5 percent for heparin). But even this risk has been reduced by avoiding the use of these drugs in patients with recent strokes, advanced cerebrovascular disease, intracranial neoplasms and severe hypertension.

A Substantial and Well-Documented Benefit Is Achieved

To understand the benefit achieved, one must appreciate the natural history of proximal deep vein thrombosis of the lower extremity (involvement of the poplitcal, femoral and iliac veins) or pulmonary embolism in a patient treated with anticoagulants alone. In this situation, anticoagulation only serves as a secondary preventive measure; it slows or stops the underlying thrombotic process and, in so doing, inhibits extension of the venous thrombosis and decreases the likelihood of pulmonary embolism or its recurrence. However, anticoagulation has no acute demonstrable effect on the original thrombus or embolus—that is, it does not alter the acute hemodynamic disturbances, nor does it affect the late or chronic pathological changes associated with the original thrombus or embolus.

The natural history of proximal deep vein thrombosis in the anticoagulated patients is to undergo organization and subsequent recanalization but with loss of normal venous valvular function. Serial venographic studies carried out during the first week in patients treated with heparin following an attack of proximal deep vein thrombophlebitis have shown that complete resolution of the venous thrombosis can be expected to occur in 10 percent or less of patients, some resolution may be evident in approximately another 15 percent to 20 percent, while the remainder (70 percent to 75 percent) either have no resolution or some progression of the underlying process.[7-15]

Pathological and radiological studies have shown that large venous thrombi that do not undergo rapid resolution are organized and ultimately recanalized but the new channel contains no valves, or where valves remain they are functionally inadequate because of cicatricial changes and anatomical disfiguration. Thus most patients are left with persistent venous hypertension in the affected extremity.[15] While the appearance of an overt and disabling postphlebitic insufficiency syndrome may be relatively uncommon, most of these patients will remain symptomatic (pain, swelling and the like) and be at permanent high risk of recurrent thrombophlebitis once anticoagulation is stopped. In the recent study by Elliott and his associates,[15] it was observed that of 25 patients treated with adequate anticoagulation alone for proximal thrombophlebitis, two died of

pulmonary embolism and two others subsequently died of malignant disease. Of the remaining 21 who were available for two-year follow-up studies, 19 were still symptomatic, with venous claudication having developed in four and venous ulcers occurring in one.

The natural history of pulmonary embolism is not as innocuous as formerly believed. Despite the view that the ultimate disappearance of the perfusion defect on lung scanning (usually during three months), suggests that the pulmonary vascular bed returns to normal both anatomically and physiologically, the course of pulmonary emboli, particularly when large or extensive, is not very dissimilar from that of the venous thrombi from which they arise.

First, there is evidence that when pulmonary hypertension is associated with an embolic episode, it is not acutely affected by heparin therapy.[2,16] Second and equally important is the observation that the pulmonary hypertension, though somewhat moderated, is still present when these patients are restudied three to five years later.[17] Even in the study that claimed that the pulmonary hypertension of acute pulmonary embolism normally resolves completely, the conclusion is based on serial observations on only two patients whose cases were followed for a month or more, and where moderately elevated pulmonary artery pressures were still evident.[16]

Pathological studies[18] have shown that pulmonary emboli frequently undergo organization and that fibrous webs and other organized residua of previous embolic episodes are often evident at autopsy. Furthermore, persistence of pulmonary perfusion defects on lung scanning is still demonstable one to seven years later in approximately 25 percent to 30 percent of the cases followed serially for periods of one to seven years,[2,16] and even in those where the perfusion defect has ultimately resolved, permanent hemodynamic disturbances and, presumably, anatomical changes may still be evident.[17]

Finally, the observations of Sasahara and his associates[19] on a permanent defect in pulmonary capillary blood volume which follows an acute embolic episode in patients treated with anticoagulation alone (discussed in the Specialty Conference "The Use of Fibrinolytic Agents," which appears in this issue) provides additional evidence that anticoagulation alone is a limited form of therapy and leaves the patient with a modest but permanent handicap. This handicap, which may not be severe enough to produce chronic cor pulmonale, nevertheless, places the patient at a distinct disadvantage should there be recurrent embolism or the subsequent development of other forms of cardiac or pulmonary disease.

In summary, a patient who is treated solely with anticoagulants for proximal deep vein thrombosis or pulmonary embolism, particularly when the latter is extensive, receives the benefit of secondary prophylaxis. However, the treatment has no significant reparative effect, and the patient is left with the following potential problems: massive pulmonary embolism, though reduced in frequency, still remains a significant threat; morbidity is usually protracted in those with massive pulmonary embolism, and persistent pulmonary hypertension frequently follows; chronic venous hypertension is the usual aftermath of proximal deep vein thrombosis as well as an increased risk for recurrent episodes of thrombophlebitis and pulmonary embolism.

These consequences can be avoided if therapy is aimed at removing an offending thrombus and embolus first so as to restore the circulation and anatomy to normal, and then preventing recurrence. The latter can be accomplished in most cases by anticoagulation but removal of the thrombus or embolus requires either a surgical procedure or enzymatic lysis. Unfortunately, the usefulness of surgical thrombectomy and the indications for embolectomy have been very limited. On the other hand, a successful enzymatic thrombectomy and embolectomy can be accomplished in a majority of the cases,[2,3,7-15] particularly when the lesion is less than 72 hours old, and this has resulted in a more rapid and satisfactory clinical improvement over that observed with heparin both for proximal deep vein thrombosis[20] and pulmonary embolism.[21,22] Even more important, however, are the observations that when successful enzymatic lysis is followed by anticoagulation to prevent recurrence, many of the late consequences described above for the more conventional therapy of thrombophlebitis[15] and pulmonary embolism[19] are avoided. Thus thrombolytic therapy when used properly in appropriately selected cases,[4,5] and in tandem with anticoagulation, offers the physician a significant advance in the therapy of proximal deep vein thrombosis including its socioeconomic considerations[23] and for the more severe forms of acute pulmonary embolism.

Under any circumstance, however, venous thrombosis and pulmonary embolism should be viewed as a single entity (pulmonary embolism is only a complication of a venous thrombosis), and the extent of both lesions should be evaluated before a definitive therapeutic decisions is made.

SOL SHERRY, MD
Professor and Chairman
Department of Medicine
Temple University School of Medicine
Philadelphia

REFERENCES

1. Sherry S, Bell WR, Duckert FH, et al: Thrombolytic Therapy in Thrombosis: A National Institutes of Health Consensus Development Conference. Ann Intern Med 93:141-144, Jul 1980; also, Br Med J 1:1585-1587, Jun 28, 1980

2. Urokinase Pulmonary Embolism Trial Study Group: A urokinase pulmonary embolism trial—A national cooperative study. Circulation 47(Suppl II):1-108, Apr 1973

3. Urokinase-Strepokinase Pulmonary Embolism Trial Study Group: Urokinase-streptokinase pulmonary embolism trial—Phase II results: A national cooperative study. JAMA 229:1606-1613, Sep 16, 1974

4. Bell WR, Meek AG: Guidelines for the use of thrombolytic agents. N Engl J Med 301:1266-1270, Dec 6, 1979

5. Marder VJ: The use of thrombolytic agents: Choice of patient, drug administration, laboratory monitoring. Ann Intern Med 90:802-808, May 1979

6. Marder VJ: Are we using fibrinolytic agents often enough? Ann Intern Med 93:136-137, Jul 1980

7. Browse NL, Thomas ML, Pim HP: Streptokinase and deep vein thrombosis. Br Med J 3:717-720, Sep 21, 1968

8. Kakkar VV, Flanc C, Howe CT, et al: Treatment of deep vein thrombosis—A trial of heparin, streptokinase and arvin. Br Med J 1:806-810, Mar 29, 1969

9. Robertson BR, Nilsson IM, Nylauder G: Thrombolytic effect of streptokinase as evaluated by phlebography of deep venous thrombi of the leg. Acta Chir Scand 136:173-180, 1970

10. Tsapogas MJ, Peabody RA, Wu KT, et al: Controlled study of thrombolytic therapy in deep vein thrombosis. Surgery 74:973-984, Dec 1973

11. Duckert F, Müller G, Nyman D, et al: Treatment of deep vein thrombosis with streptokinase. Br Med J 1:479-487, Mar 1, 1975

12. Porter JM, Seaman AJ, Common HH, et al: Comparison of heparin and streptokinase in the treatment of venous thrombosis. Am Surg 41:511-519, Sep 1975

13. Marder VJ, Soulen RL, Atichartakarn V: Quantitative venographic assessment of deep vein thrombosis in the evaluation of streptokinase and heparin therapy. J Lab Clin Med 89:1018-1029, May 1977

14. Arnesen H, Heilo A, Jakobsen E, et al: A prospective study of streptokinase and heparin in the treatment of venous thrombosis. Acta Med Scand 203:457-463, 1978

15. Elliot MS, Immelman EJ, Jeffery P, et al: A comparative randomized trial of heparin versus streptokinase in the treatment of acute proximal venous thrombosis: An interim report of a prospective trial. Br J Surg 66:838-843, Dec 1979

16. Dalen JE, Alpert JS: Natural history of pulmonary embolism, *In* Sasahara AA, Sonnenblick EH, Lesch M (Eds): Pulmonary Emboli. New York, Grune & Stratton, 1975, pp 77-88

17. de Soyza NDB, Murphy ML: Persistent postembolic pulmonary hypertension. Chest 62:665-668, 1972

18. Freiman DG: Venous thromboembolic disease in medical and malignant states, *In* Sherry S, Brinkhous KM, Genton E, et al (Eds): Thrombosis. Washington DC, National Academy of Sciences, 1969, pp 5-18

19. Sharma GVRK, Burleson VA, Sasahara AA: Effect of thrombolytic therapy on pulmonary capillary blood volume in patients with pulmonary embolism. N Engl J Med 303:842-845, 1980

20. Robertson BR: On thrombosis, thrombolysis and fibrinolysis. Acta Chir Scand Suppl 421:5-51, 1971

21. Miller GAH, Hall RJC, Paneth M: Pulmonary embolectomy, heparin and streptokinase; their place in the treatment of acute massive pulmonary embolism. Am Heart J 93:568-574, 1977

22. Ly B, Arnesen H, Eie H, et al: A controlled trial of streptokinase and heparin in the treatment of major pulmonary embolism. Acta Med Scand 203:465-470, 1978

23. O'Donnell TF, Browse NL, Burnand KG, et al: The socioeconomic effects of an ileo-femoral thrombosis. J Surg Res 22: 483-488, 1977

CASE REPORTS

Refer to: Caggiano V, Nielsen SL, Glassy FJ, et al: Immunoglobulin D myeloma: Report of a case with unusual neurological complications. West J Med 134:153-158, Feb 1981

ABBREVIATIONS USED IN TEXT

BUN = blood urea nitrogen
Hb = hemoglobin
IgD = immunoglobulin D
RER = rough endoplasmic reticulum

Immunoglobulin D Myeloma

Report of a Case With Unusual Neurological Complications

VINCENT CAGGIANO, MD
SURL L. NIELSEN, MD
FRANK J. GLASSY, MD
DAVID F. DOZIER, Jr, MD
Sacramento, California

IMMUNOGLOBULIN D (IgD) myeloma, first described by Rowe and Fahey in 1965,[1] is rare and has several features which set it apart from other forms of multiple myeloma. The IgD myeloma protein is predominantly of the λ type, greater than 90 percent of patients with the disorder have Bence Jones proteinuria; extramedullary spread and amyloidosis are frequent and survival is short.[2] We report an additional case of IgD myeloma characterized by an aggressive clinical course, hepatosplenomegaly, renal insufficiency and neurological complications. Electron microscopic studies of bone marrow are also presented. Data from three other cases of IgD myeloma found in our laboratory are also presented.

Report of a Case

A 65-year-old man was well until three weeks before admission to Mercy General Hospital on December 20, 1976, when he noted the abrupt onset of severe midback, nonradiating pain. Admittance to hospital was eventually required because of increasing severity of the back pain.

On physical examination the following findings were noted: blood pressure 140/80 mm of mercury, pulse 96 beats per minute, temperature 37°C (98.6°F), respirations 14, height 165 cm (5 ft, 4 in) and weight 80 kg (176.8 lb). The patient appeared moderately ill and had severe back pain with minimal motion in bed. Midthoracic tenderness was present to mild percussion but no deformities or masses were noted. He had powerful strength in all four extremities and straight leg raising was negative. Deep tendon reflexes were symmetrically equal and full responses were obtained to pinprick, light touch, vibratory and position sense. Gait was not tested because of the patient's discomfort. The liver was felt 4 cm and the spleen 2 cm below the costal margins. No other abnormalities were noted.

Admitting laboratory data included the following: hemoglobin (Hb) 11.5 grams per dl; packed cell volume 33.0; leukocyte count 7,800 per cu mm, with 45 percent segmented neutrophils, 5 percent bands, 3 percent metamyelocytes, 2 percent myelocytes, 44 percent lymphocytes and 1 percent plasma cells; platelet count 118,000 per cu mm; blood urea nitrogen (BUN) 48 mg per dl; creatinine 3.8 mg per dl; SGOT (serum aspartate aminotransferase; formerly serum glutamic-oxaloacetic transaminase) 74 units; SGPT (serum alanine aminotransferase; formerly serum glutamic-pyruvic transaminase) 78 units; lactic dehydrogenase (LD) 418 units and total serum protein 5.7 grams per dl, with albumin 3.8 and globulin 1.9 grams per dl. Electrolytes, calcium, phosphorus, alkaline phosphatase and bilirubin levels were normal. A 24-hour urine collection showed excretion of 5.2 grams of protein. A monoclonal peak was identified in the beta region in both serum and urine by protein electrophoresis on paper and cellulose acetate. An IgD myeloma protein in the serum and free λ light chains in both serum and urine were identified by immunoelectrophoresis. Serum im-

From the Hematology (VC) and Neurology (DFD Jr) Divisions, Department of Medicine and the Neuropathology (SLN) and Hematopathology (FJG) Divisions, Department of Pathology, Mercy General Hospital and Sutter Community Hospitals, Sacramento, and the University of California, Davis, School of Medicine.

Submitted, revised, May 14, 1980.

Reprint requests to: Vincent Caggiano, MD, Director, Sacramento Medical Foundation Blood Bank, 3142 J Street, Sacramento, CA 95816.

munoglobulin concentrations were as follows: IgG 211, IgA 13, IgM 7 and IgD 1,100 mg per dl.*

Extensive infiltration of bone marrow with plasma cells was noted on both aspirate smears and biopsy sections. Coagulation studies including bleeding time, prothrombin time, activated partial thromboplastin test, thrombin time and fibrinogen level were normal. Roentgenograms of the skeletal system showed multiple small lucencies of the skull and ribs, consistent with myeloma.

On the fourth hospital day the patient complained of numbness about the chin and mild blurring of vision in the left eye. Diminished facial sensation to pinprick and light touch around the point of the chin, covering an area of 4 cm in diameter and extending to the lower lip, and slight ptosis of the left upper eyelid were noted. Funduscopic examination, pupillary response, extraocular movements, visual fields to confrontation, speech, swallowing and mastication were normal. By the fifth hospital day the ptosis was more pronounced, diminished adduction of the left eye was apparent and horizontal diplopia was present. In addition to the apparent incomplete left third cranial nerve palsy, left mandibular motor and sensory dysfunction were also present, rather than an isolated mental nerve palsy, as initially suspected. There was deviation of the jaw to the left on opening the mouth, defective contraction of the left masseter muscle when the patient was asked to clench his teeth, and diminished to absent facial sensation in the distribution of the mandibular branch of the left trigeminal nerve. Computerized brain tomography showed only changes consistent with slight cortical atrophy and a technetium Tc 99m radionuclide brain scan showed no abnormalities. A myelogram showed a partial extradural block at the T3-T4 level. Unfortunately, the cerebrospinal fluid was not examined.

A treatment plan involving multiagent chemotherapy[3,4] and palliative radiation therapy to the thoracic spine and base of the brain was outlined, but the patient consented only to limited chemotherapy. Thus, on the sixth hospital day a four-day course of melphalan, 10 mg per M^2 per day and prednisone, 60 mg per M^2 per day was begun. No objective improvement was noted; instead there was progression of disease with decreasing renal function, increasing back pain, persistence of partial left third cranial nerve paralysis, left mandibular motor and sensory dysfunction and intermittent obtundation. The patient also had difficulty in voiding, and an indwelling catheter was required. Serum calcium levels and viscosity were normal, as were electrolytes. Transfusions of three units of red blood cells were required. On the 25th hospital day bilateral pneumonitis developed. At that time the Hb was 10.1 grams per dl, leukocyte count 2,900 per cu mm, with 48 percent neutrophils and platelet count 82,000 per cu mm. The BUN was 126 mg per dl and creatinine 13.4 mg per dl, the patient having also refused peritoneal dialysis, hemodialysis or plasmapheresis. Despite appropriate antibiotic therapy and careful attention to fluid and electrolyte management, his condition worsened and the patient died on the 29th hospital day.

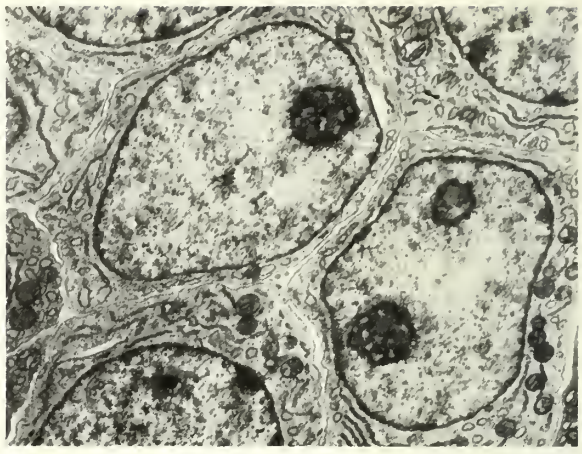


Figure 1.—Bone marrow electron micrograph. Primitive plasma cells containing large nucleoli, minimal fine nuclear chromatin and cytoplasm with distinct parallel bands of rough endoplasmic reticulum are identified. Mitochondria are seen in the right cell. The primitive nucleus and relatively well-developed cytoplasm are characteristic of nuclear-cytoplasm asynchrony. (Reduced from magnification ×6,300.)

Pathological Findings

Bone Marrow

Plasma cells made up 68 percent of all hematopoietic cells on bone marrow aspirate smears and biopsy sections as viewed under light microscopy. The majority were medium to large plasma cells with minimal cytoplasm and primitive-appearing nuclei with finely delicate chromatin with small or indistinct nucleoli. An occasional binucleate plasma cell was noted. The erythroid, myeloid and megakaryocytic series were morphologically normal.

Electron microscopic examination showed the

*The IgD quantitation was done by Hans L. Spiegelberg, MD, Department of Immunopathology, Scripps Clinic and Research Foundation, La Jolla, California..

bone marrow to consist predominantly of plasma cells with cytoplasm containing many parallel arrays of flattened rough endoplasmic reticulum (RER) and prominent Golgi apparati. Some of the cisternae of RER were dilated and contained a finely granular material of very light electron density. No crystalline material was seen. The nuclei had little chromatin aggregation and prominent nucleoli (Figure 1). These features indicated pronounced plasma cell nuclear-cytoplasmic asynchrony according to the criteria of Graham and Bernier.[5,6]

Postmortem Examination

Bronchopneumonia, pulmonary edema and pleural effusions appeared to be the terminal events. Widespread infiltrates of plasma cells were found in many sites including pleura, pericardium, liver, spleen, perirenal and periadrenal fat and retroperitoneal lymph nodes. Vertebral involvement was associated with extension into the epidural space, permeation of the dura and formation of a circumscribed intradural mass at the fourth thoracic level (Figure 2). Compression but not invasion of the spinal cord at this level corresponded to the mass lesion. There was extensive involvement of the sphenoid bone and cavernous sinus, especially on the left. Within the sinus, the infiltrate surrounded the venous channels, invaded the carotid artery adventitia and compressed cranial nerves (Figure 3). Involvement about the area of the left foramen ovale was not clearly observed. Petechial hemorrhages were noted in the brain stem and cerebrum as well as in soft tissues. Many renal tubules with compressed epithelial cells were dilated by eosinophilic amorphous material that contained elongated, eosinophilic, rod-like structures, suggesting a crystalline character. Nodular infiltrates of plasma cells were noted in the perirenal fat and fat of the renal pelvis. Amyloidosis was absent.

Discussion

Multiple myeloma has an annual incidence of about 3.0 per 100,000 population,[7] and IgD myeloma accounts for less than 3 percent of all myelomas.[2] To date, only 161 cases of IgD myeloma have been reported.[1,2,8-21] In the authors' experience at Mercy General and Sutter Community Hospitals from 1969 through 1979, 125 patients with plasma cell disorders were examined and four patients with IgD myeloma, one of them previously reported,[8] were identified (Table 1).

Neurological complications occur in over a third of patients with multiple myeloma, the most frequent abnormalities being nerve root pain, spinal cord or cauda equina compression, due either to extradural deposits of myeloma or collapsed vertebrae.[22] The patient described in the present report had vertebral involvement with extension into the epidural space, infiltration of the dura and formation of an intradural mass at the T4 level. Intracranial involvement is uncommon and generally presents in one of several forms—cases with myeloma deposits in the bone of the base of the skull, producing single or multiple cranial nerve palsies; cases simulating intracranial tumor syndromes, and cases with intraorbital involvement.[23] In one review, only two of 179 patients with myeloma (1.1 percent) had

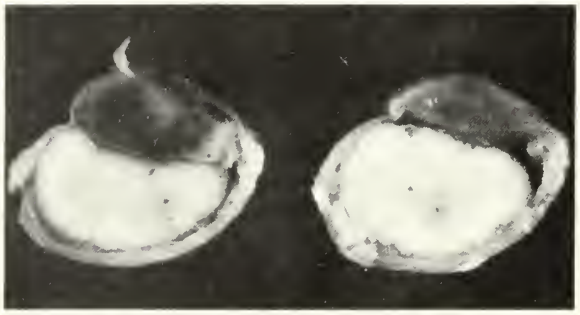


Figure 2.—Horizontal section of spinal cord at T4 level, showing distortion of the cord by the large intradural myeloma mass.

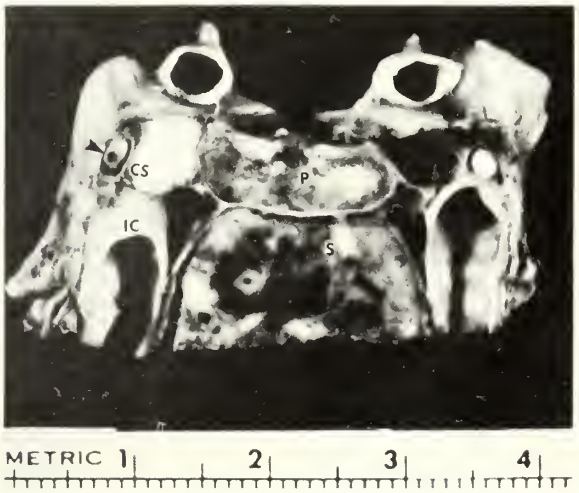


Figure 3.—Coronal section through the sella turcica and adjacent structures shows myelomatous infiltrates involving sphenoid bone and sinus (S), cavernous sinus (CS) and internal carotid artery sheath (IC). Lateral to the carotid, the infiltrate obscures the fourth, sixth and ophthalmic division of the fifth cranial nerves. Note the compression with focal hemorrhage of the left third cranial nerve (arrow). The pituitary (P) is uninvolved.

cranial nerve involvement.[24] Myeloma within the body of the sphenoid bone and in the apex of the petrous bone are the most common sites of involvement and the sixth, seventh, eighth and fifth cranial nerves most often afflicted, in that order.[23] In our patient, myeloma involved the sphenoid bone and the cavernous sinus. Within the latter, the infiltrate surrounded the vascular channels, invaded the carotid artery adventitia and compressed the cranial nerves. As others have commented, we cannot explain why the fourth and sixth nerves were spared.[25] The motor fibers of the fifth nerve pass with the mandibular branch, which does not traverse the cavernous sinus. However, compression of the nerve is possible along its course at the base of the skull, very probably in the region of the left foramen ovale. Isolated paralysis of the third nerve or the mandibular branch of the fifth nerve has been described in other patients with myeloma,[23,24,26] but to the best of our knowledge this combination of cranial nerve involvement, as clinically evident in our patient, has not been described. Direct arterial invasion by myeloma has been previously reported once, interestingly, in a case of IgD myeloma.[16]

Extramedullary spread of IgD myeloma has been noted in many sites, including the gastrointestinal tract, lymph nodes, liver, spleen, pleura, pericardium, genitalia, breasts, skin, skeletal muscles and heart. Involvement of kidneys was noted at autopsy in 19 of 33 patients with IgD myeloma described by Jancelewicz and co-workers,[2] and renal failure was the most common cause of death. The patient in the present report had extensive extramedullary spread of myeloma that included the kidneys, and the cause of death was renal failure complicated by pneumonitis. The single most important factor influencing prognosis is the level of the BUN or creatinine at the time of diagnosis.[27-29] Attempts to treat acute and chronic renal failure in patients with myeloma by peritoneal dialysis, hemodialysis and plasmapheresis have been successful.[29-32] Unfortunately, our patient did not consent to any of these forms of treatment.

The ultrastructural study of the bone marrow did not detect any abnormality specific for IgD myeloma. Most of the plasma cells had large nuclei, prominent nucleoli, well-developed endoplasmic reticulum, dilated cisternae and large Golgi areas. Pronounced nuclear-cytoplasmic asynchrony was observed both by routine light microscopy and electron microscopy.[5,6] Distinctive ultrastructural features of myeloma cells previously described[19,33,34] were not seen.

Certain patterns of clinical manifestation of multiple myeloma are related to the class and type of M component. Thus, hyperviscosity is most frequent in IgG3 myeloma,[35] the development of hypercalcemia is significantly more frequent in IgG2 myeloma,[36] the presence of λ-type Bence Jones proteinuria has an adverse influence on survival,[37] and myelomatous ascites is most often associated with IgA myeloma.[38]

A distinct clinical pattern of IgD myeloma has

TABLE 1.—*Cases of Multiple Myeloma (125) Seen at Mercy General and Sutter Community Hospitals (1969-1979)*

Class of M Component	Number of Cases: Light-Chain Type k	λ	Total	Percent
IgG	51	22	73	58.4
IgA	16	14	30	24.0
BJP	11	7	18	14.4
IgD	1	3	4	3.2
TOTAL	79	46	125	100.0

TABLE 2.—*Four Patients With IgD Myeloma Seen at Mercy General and Sutter Community Hospitals (1969-1979)*

Data	Patients 1*	2	3†	4
Age (yr), Sex	65, M	68, M	46, M	70, M
Survival (mo)	1.0	1.5	87.0	12‡
Admission BUN level (mg/dl)	48.0	117.0	22.0	16.0
Admission creatinine level (mg/dl)	3.8	7.1	0.7	1.0
Plasma cell asynchrony§	Pronounced	Pronounced	Slight	Slight
Light-chain type	Lambda	Lambda	Lambda	Kappa

BUN = blood urea nitrogen

*Patient described in present report.
†Patient reported previously.[8]
‡Patient still alive.
§Assessed by light and electron microscopy in patients 1 and 2, and by light microscopy only in patients 3 and 4.

also emerged. IgD myeloma represents an aggressive form of myeloma with a median survival of only nine months.[2,39] The total serum protein value is often low and the level of M component was lower than 2.0 grams per dl in 61 percent of reported patients, in clear contrast to the high levels of IgG and IgA M components.[2] In a review of 133 cases of IgD myeloma, the male to female ratio was 3:1; 65 percent of the patients were younger than 60 years at the time of diagnosis; more than half of the patients had lymphadenopathy, hepatomegaly or splenomegaly, and extraosseous spread and amyloidosis were frequent. Bence Jones proteinuria was found in 92 percent and Bence Jones proteinemia in 71 percent of the group.[2] In contrast to other forms of myeloma, the IgD myeloma protein was of the λ light-chain type in 90 percent of patients.

Our limited experience with four patients illustrates the variability of the clinical course of IgD myeloma (Table 2). In the absence of staging criteria for IgD, as have been developed for IgG, IgA and light-chain myelomas,[40] it seems reasonable to use the rating system devised for assessing clinical extent of disease and plasma cell asynchrony.[5] In agreement with Graham and Bernier,[5,6] the degree of asynchrony was proportional to the extent of disease as judged by clinical criteria.

Summary

A case of IgD λ myeloma characterized by Bence Jones proteinemia and proteinuria, hepatosplenomegaly, extensive extramedullary spread and renal failure with myeloma of the kidneys is presented. Unusual neurological complications included cranial nerve palsies that involved the left third nerve and the mandibular branch of the left fifth nerve. Extensive infiltration of the sphenoid bone with extension into the cavernous sinus was present. The pronounced nuclear-cytoplasmic asynchrony observed by both light and electron microscopy correlated with the extent and clinical aggressiveness of the disease. Because the level of the M component is often low and a monoclonal peak may not be apparent, the diagnosis of IgD myeloma may be overlooked unless appropriate application of immunoelectrophoresis is made to strengthen the clinical impression. Our community hospital experience confirms the usefulness of this laboratory procedure.

REFERENCES

1. Rowe DS, Fahey JL: A new class of immunoglobulins—I. A unique myeloma protein. J Exp Med 121:171-184, 1965

2. Jancelewicz A, Takatsuki K, Sugai S, et al: IgD multiple myeloma—Review of 133 cases. Arch Intern Med 135:87-93, 1975

3. Lee BJ, Sahakian G, Clarkson BD, et al: Combination chemotherapy of multiple myeloma with alkeran, cytoxan, vincristine, prednisone and BCNU. Cancer 33:533-538, 1974

4. Case DC, Lee BJ, Clarkson BD: Improved survival times in multiple myeloma with melphalan, prednisone, cyclophosphamide, vincristine and BCNU: M-2 protocol. Am J Med 63:897-903, 1977

5. Graham RC, Bernier GM: The bone marrow in multiple myeloma: Correlation of plasma cell ultrastructure and clinical state. Medicine 54:225-243, 1975

6. Bernier GM, Graham RC: Plasma cell asynchrony in myeloma: Correlation of light and electron microscopy. Semin Hematol 13:239-245, 1976

7. McPhedran P, Heath CW Jr, Garcia J: Multiple myeloma incidence in metropolitan Atlanta, Georgia: Racial and seasonal variations. Blood 39:866-873, 1972

8. Fishkin BG, Glassy FJ, Hattersley PG, et al: IgD multiple myeloma: A report of five cases. Am J Clin Pathol 53:209-214, 1970

9. Tichy M, Hrncir Z, Pola V, et al: Immunochemical analysis of IgD-lambda paraprotein in myeloma. Neoplasma 21:487-491, 1974

10. Jako J, Viragh S, Boga M, et al: A case of IgD-lambda myeloma. Haemotologia 9:261-278, 1975

11. Kyle RA: Multiple myeloma:. Review of 869 cases. Mayo Clinic Proc 50:29-40, 1975

12. Isobe T, Ikeda Y, Ohta H, et al: IgD myeloma—A clinical study of 9 cases. Acta Haematol Jap 39:319-328, 1976

13. Harisdangkul V, Srichaikul T: A case of IgD myeloma with clinical manifestation resembling malignant lymphoma. J Med Assoc Thai 59:333-338, 1976

14. Cooney T, Sweeney T: The hen's tooth: Arterial aneurysm resulting from invasion by IgD myeloma cells. Irish J Med Sci 146:295-297, 1977

15. Dandelot JB, Lees O, Sauger F: Paralysie isolée du XII révélatrice d'un myéloma à IgD. La Nouvelle Presse Med 6:853, 1977

16. Toth J: IgD myeloma: A case report. Can Med Assoc J 116:1235-1236, 1238, 1977

17. Udoji WC, Pemmaraju S: IgD myeloma with myelofibrosis and amyloidosis. Arch Pathol Lab Med 101:10-13, 1977

18. Burlando L, Milone S, Acguarone N, et al: Gamma-D-mieloma: Segnalazione di due casi. Pathologica 70:39-52, 1978

19. Ioachim NJ, McKenna PJ, Halperin I, et al: IgD myeloma: Immunology and ultrastructure. Ann Clin Lab Sci 8:209-218, 1978

20. Knowles DM, Halper JA, Trokel S, et al: Immunofluorescent and immunoperoxidase characteristics of IgD λ myeloma involving the orbit. Am J Ophthalmol 85:485-494, 1978

21. Valenzuela R, Govindarajan S, Tubbs R, et al: IgD myeloma: Report of a case with unusual clinical and immunologic features. Am J Clin Pathol 72:246-250, 1979

22. Silverstein A, Doniger DE: Neurologic complications of myelomatosis. Arch Neurol 9:534-544, 1963

23. Clarke E: Cranial and intracranial myeloma. Brain 77:61-81, 1954

24. Williams HM, Diamond HD, Craver LF, et al: Neurological complications of lymphomas and leukemias. Springfield, IL, Charles C Thomas, 1959

25. Sundaresan N, Noronha A, Hirschauer J, et al: Oculomotor palsy as initial manifestation of myeloma. JAMA 238:2052-2053, 1977

26. Nobler MP: Mental nerve palsy in malignant lymphoma. Cancer 24:122-127, 1969

27. Medical Research Council: Report of the first myelomatosis trial—Part I. Analysis of presenting features of prognostic importance. Br J Haematol 24:123-139, 1973

28. Southeastern Cancer Study Group: Treatment of myeloma. Comparison of melphalan, chlorambucil, and azathioprine. Arch Intern Med 135:157-162, 1975

29. Kyle RA, Elveback LR: Management and prognosis of multiple myeloma. Mayo Clinic Proc 51:751-760, 1976

30. Leech SH, Polesky HF, Shapiro FL: Chronic hemodialysis in myelomatosis. Ann Intern Med 77:239-242, 1972

31. Feest TG, Burge PS, Cohen SL: Successful treatment of myeloma kidney by diuresis and plasmapheresis. Br Med J 1: 503-504, 1976

32. Vaziri NB, Goldman R, Schultze RG, et al: Maintenance hemodialysis in myeloma kidney disease. West J Med 126:91-94, 1977

33. Maldonado JE, Brown AL, Bayrd ED, et al: Cytoplasmic and intranuclear electron-dense bodies in the myeloma cell. Arch Pathol 81:484-500, 1966

34. Brecher G, Tanaka Y, Malmgren RA, et al: Morphology and protein synthesis in multiple myeloma and macroglobulinemia. Ann NY Acad Sci 113:642-653, 1954

35. Virella G, Hobbs JR: Heavy chain typing in IgG monoclonal gammopathies with special reference to cases of serum hyperviscosity and cryoglobulinemia. Clin Exp Immunol 8:973-980, 1971

36. Schur PH, Kyle RA, Bloch KJ, et al: IgG subclasses: Rela-

tionship to clinical aspects of multiple myeloma and frequency distribution among M-components. Scand J Haematol 12:60-68, 1974

37. A Cooperative Study by Acute Leukemia Group B: Correlation of abnormal immunoglobulin with clinical features of myeloma. Arch Intern Med 135:46-52, 1975

38. Koeffler HP, Cline MJ: Multiple myeloma presenting as ascites. West J Med 127:248-250, 1977

39. Pruzanski W: Clinical manifestations of multiple myeloma: Relation to class and type of M component. Can Med Assoc J 114:896-897, 1976

40. Durie BG, Salmon SE: A clinical staging system for multiple myeloma. Cancer 36:842-854, 1975

Refer to: Ciferri F: Human pulmonary dirofilariasis in the West. West J Med 134:158-162, Feb 1981

Human Pulmonary Dirofilariasis in the West

FLAVIO CIFERRI, MD, MPH
Los Angeles

IN NATURE, the heartworm *Dirofilaria immitis* is transmitted primarily from dog to dog by mosquitoes carrying infective-stage larvae. In humans pulmonary dirofilariasis may develop when an infective larva is introduced into the abnormal human host, survives to become an adult filaria and then lodges in a branch of the pulmonary artery causing a small infarct. This is usually detected as a *coin* lesion in radiographs, surgical specimens or autopsies.

Fifty indigenous cases of this disease have been reported in the literature in the United States since its first description by Dashiell[1] in 1961. The geographic distribution of these cases (Figure 1) roughly parallels that of dog heartworm infection in this country.[2(pp1-2)] Most cases in humans have occurred along the Atlantic and Gulf coasts, from Massachusetts to Texas. This report describes the first documented case of human pulmonary dirofilariasis acquired in California and discusses its relationship to some of the epidemiologic factors that influence the transmission of this zoonosis to humans.

From the Department of Medicine, Southern California Permanente Medical Group, Los Angeles.

Submitted March 10, 1980.

Reprint requests to: Flavio Ciferri, MD, MPH, 1526 North Edgemont Street, Los Angeles, CA 90027.

Figure 1.—Geographic distribution of human cases of pulmonary dirofilariasis in the United States, 1961-1979.

Report of a Case

A 67-year-old man, a retired machinist, was seen at our facility in Fontana, California, in September 1978 for a suspected prostatic malignancy. Except for the prostate, findings on the physical examination and the laboratory data were within normal limits. An x-ray study of the chest on September 9 showed no abnormalities. Needle biopsy of the prostate disclosed adenocarcinoma, stage IIIB. Surgical operation was declined, and the patient was treated with radiation from October 11 to December 8. He remained essentially asymptomatic—except for an eruption of herpes zoster on the left side of his chest on December 20—until January 12, 1979, when he reported that he had had a respiratory illness for ten days. It was characterized by coughing that produced whitish sputum, chest discomfort, malaise and fever. He was treated empirically with tetracycline for a week, but there was no symptomatic improvement. On January 22 a physical examination showed a temperature of 38°C (100.4°F) and bilateral moist rales; an x-ray study of the chest showed a 2-cm nodular lesion in the right lung field. He was treated with ampicillin for another week. There was symptomatic improvement, but the lung lesion remained unchanged. An extensive workup, which included tomograms, blood chemistry studies, sputum cytology, bronchoscopy, transbronchial biopsy and so on, failed to clarify the nature of this lesion. On March 12 a thoracotomy was carried out and the right lower lobe removed. At section, a firm, tan-white nodular mass measuring 1.8 × 1.5 cm was found, which on histologic examination contained several transverse sections of a sexually

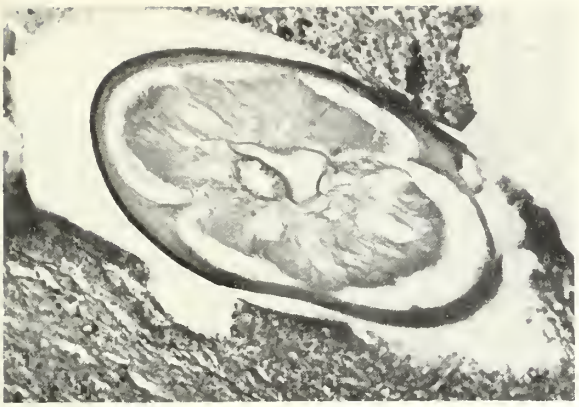


Figure 2.—Cross section of an adult male *Dirofilaria immitis*. (Hematoxylin-eosin stain, reduced from magnification ×560).

mature male *Dirofilaria immitis.** It measured between 225 and 250 μ in diameter, had a smooth thick cuticle, prominent internal ridges, thick muscular masses and one reproductive tube (Figure 2). No peripheral eosinophilia was detected preoperatively. Postoperatively, the total eosinophil count was 308 per cu mm, examination of venous blood by the Knott concentration and Millipore filtration methods detected no microfilariae and a serological test for filariasis was negative.

Epidemiology

Four major factors influence the frequency with which dirofilariasis is likely to occur in a human population and its potential distribution in a given geographic area. These are the size of the dog population, the prevalence of dirofilariasis in that population, the dynamics of the vector mosquito and the behavior of human beings. We shall discuss each factor in relation to the index case, in an attempt to place it in the proper epidemiologic context.

Human behavior. This behavior includes, in a broad sense, those living habits or travel modalities, or both, that are likely to expose people to the bite of infected mosquitoes. The patient was born in Vancouver, Canada, and immigrated to California in 1929. He lived in San Francisco until 1970, when he retired to Lake Combie in Placer County, California, where he lived until October 1977. Between 1970 and 1977 he visited Nevada, Montana, Oregon and Washington on short fishing trips. He has never visited any of the eastern or southern states. In October 1977 the patient moved to Hemet, Riverside County, and in 1978 he made two trips between Southern and Northern California. He left Hemet on April 8, going to his former home in Lake Combie where he remained until August 27, when he returned to Hemet. Between October 11 and December 8 he visited Los Angeles for radiation treatments. He then made a short visit to Auburn, Sacramento and Richmond over the Christmas holiday, returning to Hemet on December 25, where he has remained to date.

The worm removed during the operation was estimated to be between five and seven months old. Counting that many months back from the onset of his illness in January 1979, it appears that the patient was at Lake Combie when he acquired the infection. This supposition is reinforced by the fact that his home there is located among tall oaks on the shore of the lake, which is actually a reservoir created by a dam on the Bear River. This is a small, private, rural community, 13 miles north of Auburn and 3 miles from the nearest market, that consists of several single homes placed along the wooded shores. Dogs and mosquitoes are abundant there. By contrast, his home in Hemet is located in a trailer park situated just outside the city limits, in the open and dry environment typical of Southern California's semidesert. No dogs are present in the immediate vicinity.

Dog population. While *D immitis* has been found in cats, wolves, foxes, and coyotes,[2(pp6-13)] dogs remain its most important reservoir hosts. Therefore, it would seem that once the infection becomes established, the larger the canine population the greater the possibility of transmitting dirofilariasis to other dogs or to humans. In Placer County the number of licensed dogs[3] grew from 2,366 in 1970 to 11,081 in 1976 (up 368.3 percent), while the human population[4] grew from 77,632 to 95,100 (up 22.5 percent). This resulted in a reduction of the man-to-dog ratio from 32.8 to 8.5. The same sources indicate that in California as a whole, the licensed canine population grew 185 percent between 1960 and 1976, whereas the human population increased by only 35 percent. As a result, the man-to-dog ratio in the state decreased from 25.2 to 12.0 during that period. While the number of dog licenses does not

*Dr. Lawrence R. Ash of the School of Public Health, University of California, Los Angeles, and Dr. Paul C. Beaver of the Department of Tropical Medicine, Tulane University, New Orleans, confirmed the identification of the worm.

TABLE 1.—*California Veterinary Medical Association Heartworm Survey, 1977*

CVMA District Number	Number of Cases Reported Per Year 1974	1975	1976	1977	Total
1	3	4	3	3	13
2	2	7	7	12	28
4	..	1	86	56	143
5	..	..	119	..	119
6	61	103	201	213	578
7	..	3	23	55	81
8	3	21	23	70	117
10	2	..	1	3	6
TOTAL	71	139	463	412	1,085

TABLE 2.—*Average Adult Female* Culex Tarsalis *Per Trap Night*

County	1979	1978	1977	No. of Weeks Sampled	Disease Week Numbers
Sacramento-Yolo (suburban)	2.95	1.22	0.50	11	16-26
Sutter-Yuba (rural)	2.95	2.51	1.04	12	15-26

necessarily reflect the actual size of the canine population, these data do suggest that in California the dog population has been growing at a much faster rate than the human population, providing a substantial pool of potential hosts for *D immitis*.

The prevalence of canine dirofilariasis. In the United States the prevalence of canine dirofilariasis varies considerably from state to state,[5] with generally high rates found in the eastern seaboard, along the Gulf of Mexico and the Mississippi basin. Surveys done by McGreevy and associates[6] in Northern California before 1970 showed very little canine dirofilariasis. They found no infection among 515 dogs taken from pounds in five Northern California counties (Merced, Napa, Sacramento, San Joaquin and Yolo) and only one infection with *D immitis* among 800 beagles reared at the Radiation Laboratory of the University of California at Davis.

Reviewing the records of the School of Veterinary Medicine at the University of California at Davis between 1957 and 1968, they found only 12 autochthonous cases, an average of about one case per year. Interestingly, 4 of these 12 dogs had come from Placer County, while each of the remaining 8 dogs had come from a different county, suggesting that Placer County already may have been a focus of infection. When Wood[7] carried out the survey of the records from 1968 to 1975, he found 219 cases, an average of 30 cases per year.

Weinmann and Garcia[8] stated the Asher Veterinary Clinic in Redding had diagnosed 20 cases of canine dirofilariasis in just the first six months of 1974. They also found a high rate of infection among wild coyotes (43 of 115) trapped between October 1975 and February 1976 at 15 different sites within a 50-km radius of Placerville, in El Dorado County.[9] Significantly, 22 of these infected coyotes were trapped at sites located between Placerville and Auburn. Hansen[10] reported that 50 cases had been diagnosed in the summer of 1977 in San Mateo County, where previously only one or two cases per year were seen.

Unpublished data collected by the California Veterinary Medical Association in 1977 (Table 1) show that there has been a steady increase in the number of heartworm cases reported each year by their districts; between 1974 and 1977 the yearly number of cases grew from 71 to 412. District number 6, which includes Butte, Glenn, Lassen, Nevada, Plumas, Shasta, Sierra, Tehama and Yuba Counties reported the highest number of cases—a total of 578 for the four years covered by the survey. This district is located north of district number 5, which reported the next largest number, 119 cases, for the year 1976. Although the district includes Colusa, El Dorado, Sutter, Yolo, Sacramento and Placer Counties, all the cases were reported from El Dorado County by the Placerville Veterinary Clinic, which stated in its letter that there were 119 positive tests out of 1,035 done in 1976, an 11 percent prevalence of infection. In March 1979, Jackson[11] conducted a survey among veterinarians attending a seminar in Redding: 21 respondents indicated that a total of about 450 cases of heartworm infection had been seen during the previous year. All but two of these were from north central California, close to the Oregon state line. The other two cases were from Palo Alto in San Mateo County.

Mosquito dynamics. Some 60 species of mosquitoes in six genera are capable of supporting the development of *Dirofilaria immitis* larvae to the third (infective) stage,[12] and at least ten of these species (four *Aedes,* four *Culex,* two *Anopheles*) exist in California. The disease-vector relationships of these mosquitoes are still uncertain, but

Aedes sierrensis and *Aedes dorsalis* are considered important vectors.[8] In any event, it would seem that the higher the density of the vector mosquito population, the greater the chances for canine and human transmission of *D immitis*.

Mosquito surveys from Placer County for 1978, the year when the patient presumably acquired the infection, are unavailable. However, data provided by the Vector Biology and Control Section of the California Department of Health Services from four valley counties adjoining Placer to the west and the south (Table 2) indicate that mosquito population levels, as measured by *Culex tarsalis* females, in 1978 and 1979 were three to six times higher than for comparable periods in 1977. In 1978 adult female *C tarsalis* night trap collection averages were 1.22 in the Sacramento-Yolo suburban area and 2.51 in the Sutter-Yuba rural area, compared with 0.50 and 1.04, respectively, for 1977. In 1979 mosquito collections for these two areas were even higher, reaching averages of 2.95 mosquitoes per trap night.

In the Central Valley of California seasonal light trap indices for *C tarsalis* females in 1978 were higher in 80 percent of the districts compared with 1977, and in 37 percent compared with 1969, the last year when heavy snowfalls and rains had caused widespread flooding in the state.[13]

Although *C tarsalis* is only one of the potential vectors of *D immitis*,[12] and its population dynamics do not necessarily reflect the activities of other potential vectors in California, these data indicate that very high levels of some mosquito populations developed in the state in 1978 to 1979, owing to increased availability of water.

Discussion

Epidemiologic data and circumstantial evidence regarding the case reported here suggest that the most likely time and place for the acquisition of infection with *Dirofilaria* was the summer of 1978 in Lake Combie, where the patient was exposed to an environment eminently suitable for the transmission of this zoonosis to humans. This is an area where canine dirofilariasis apparently has been present for many years, althought probably at a low level. Recent studies have shown that during the past decade there has been a definite increase in the prevalence of documented canine dirofilariasis in adjoining areas. That the increase is real and not due to greater awareness or improved detection is supported by the fact that both the data of McGreevy and associates and those of Wood were derived from the same source, namely the School of Veterinary Medicine of the University of California at Davis.

Examination of wild coyotes also indicates that the disease is present in the wild, at least in El Dorado County. Coyotes therefore may represent an important reservoir for the transmission of *D immitis* not only to dogs but to humans as well. In addition, the meteorological events that took place in 1978 and 1979 apparently favored the development of large populations of mosquitoes, which may have aided the spread of heartworm disease in the canine population. The patient recalls that in Lake Combie one dog belonging to a neighbor had died in the summer of 1978 of apparent heartworm disease and three other dogs had become ill in previous years and had to be destroyed. His wife had also bitterly complained that in the summer of 1978 mosquitoes were at their worst. The development of very high mosquito densities in turn could have facilitated the accidental transmission of *D immitis* to humans. Because high levels of mosquito activity continued through 1979, it is at least theoretically possible that human transmission of this disease may still occur.

Conclusions

While it is hazardous to make generalizations based on a single case, the findings suggest that the first documented occurrence of human pulmonary dirofilariasis in California may not have been a simple accident but, rather, the result of the coalescence of several epidemiologic factors: the interactions of an expanding dog population, an increasing prevalence of canine dirofilariasis, high levels of mosquito activity and adequate human exposure in a specific area where transmission of this zoonosis to humans could take place. Because available data suggest that several Northern California counties may have become established foci of heartworm infection, the likelihood that more cases of human pulmonary dirofilariasis could occur, if circumstances remain the same, is good.

Therefore, physicians in the west are urged to include this possibility in the differential diagnosis of solitary pulmonary nodules, as it is now recommended in the eastern United States, and pathologists should thoroughly section these nodules, as

multiple-step sections may be required to detect the worm.[14] It may also be appropriate to initiate a public health campaign directed toward the education of pet owners and the control of this disease in dogs, as suggested by Hansen.[10]

Summary

A 67-year-old man, under treatment for adenocarcinoma of the prostate since September 1978, was found to have a mild respiratory illness in January 1979. An x-ray study of the chest, which had shown no abnormalities in September 1978, now showed a *coin* lesion in the right lower lobe. When noninvasive techniques failed to clarify the nodule's cause, the affected lobe was excised. The nodule contained an adult male *Dirofilaria immitis*. Epidemiologic data indicate that the patient probably acquired the infection in Lake Combie, Placer County, California, in the summer of 1978. It is postulated that this event was the result of increasing prevalence of heartworm infection in an expanding canine population, high levels of mosquito densities in 1978 and the proper human exposure. Available data suggest that in some areas of the western states conditions are suitable for the transmission to humans of this zoonosis and, therefore, physicians are urged to include this possibility in the differential diagnosis of solitary pulmonary nodules.

REFERENCES

1. Dashiell GF: A case of dirofilariasis involving the lung. Am J Trop Med Hyg 10:37-38, Jan 1961

2. Otto GF: Changing geographic distribution of heartworm disease in the United States (pp 1-2); and Occurences of the heartworm in unusual locations and in unusual hosts (pp 6-13), *In* Morgan HC, et al (Eds): Proceedings of the Heartworm Symposium '74. Bonner Springs, Kansas, Veterinary Medicine Publishing Co., 1975

3. Annual Report of Local Rabies Control Activities. State of California, Department of Health Services, 1960-1976

4. California Statistical Abstract 1976. State of California, Documents Section, Table B-5, p 8

5. Otto GF: Epizootiology of canine heartworm disease. *In* Bradley RE (Ed): Canine Heartworm Disease: The Current Knowledge. Gainesville, FL, University of Florida, Dept Vet Sc, Inst Food Agr Sc, 1972, pp 1-15

6. McGreevy PB, Conrad RD, Bulgin MS, et al: Canine filariasis in Northern California. Am J Vet Res 31:1325-1328, Jul 1970

7. Wood G, quoted in American Heartworm Society Bull 5:4, Jul 1979

8. Weinmann CJ, Garcia R: Canine heartworm in California, with observations on *Aedes sierrensis* as a potential vector. Cal Vector Views 21:45-50, Aug 1974

9. Weinmann CJ, Garcia R: Coyotes and canine heartworm in California. J Wildlife Dis 16:217-221, Apr 1980

10. Hansen CP: The sudden rise of dog heartworm (*Dirofilaria immitis*) to a serious pest level in San Mateo County. Proc Cal Mosq Vect Cont Assoc 46:15-16, Jan-Feb 1978

11. Jackson R, quoted in American Heartworm Society Bull 5: 4, Jul 1979

12. Ludlam KW, Jachowski LA Jr, Otto GF: Potential vectors of *Dirofilaria immitis*. J Am Vet Med Assoc 157:1354-1359, Nov 1970

13. Reeves WC, Milby MM: Encephalitis viral activity and vector populations in California—Present and future concerns. Proc and Papers of the 47th Annual Conference of the Cal Mosq Vect Cont Assoc 47:1-6, Aug 1979

14. Harrison EG Jr, Thompson JH Jr: Dirofilariasis of human lung. Am J Clin Pathol 43:224-234, Mar 1965

Refer to: Murray BJ: Severe lactic acidosis and hypothermia. West J Med 134:162-166, Feb 1981

Severe Lactic Acidosis and Hypothermia

BRIAN J. MURRAY, MD, *San Diego*

SURVIVAL OF PERSONS with severe lactic acidosis and a pH of less than 6.9 is unusual. In general, mortality approaches 100 percent for patients with a pH of less than 6.9 or a lactate level of greater than 13 mEq per liter.[1-3] Although there are case reports of patients surviving with a pH of less than 6.9,[4-6] there are no cases reporting survival with a lactate level of greater than 20 mEq per liter and a pH as low as 6.67, as occurred in this patient. Survival was more probable in this woman because of concordant hypothermia. Hypothermia is known to decrease the metabolic rate and, consequently, allows a patient to tolerate better inactivation of vital intracellular enzymes during acidosis. The patient's clinical features were well correlated to the hypothermia.

Report of a Case

A 49-year-old woman was brought into the emergency room after she was found lying on the floor of her apartment semicomatose. She was able to give a limited history and complained of vague abdominal pains and two to three days of nausea and vomiting. She gave no history of loss of consciousness, diabetes mellitus, recent trauma or history of toxic ingestions. A review of hospital records disclosed that she had a history of chronic alcohol abuse, presumed alcoholic liver disease, folate-deficiency anemia, schizophrenia and dementia.

Physical Examination

In the emergency room her blood pressure was 88/60 mm of mercury while supine. Her pulse was 88 per minute and regular, respirations were 36 per minute and her temperature by rectal

From the Department of Medicine, Mercy Hospital and Medical Center, San Diego.

Submitted revised, May 13, 1980.

Reprint requests to: Brian J. Murray, MD, University of California, San Diego, Q-039, La Jolla, CA 92093.

probe thermocouple thermometer was 30.5°C (87.0°F). There was no evidence of a shivering reflex present.

The patient was lethargic with Kussmaul respirations. She was oriented to name and place. She had dry mucous membranes, and skin turgor was poor. Her weight was 66 kg (145.2 pounds). Blood pressure while sitting was not palpable or audible. There was no adenopathy and integument was unremarkable except for the noted hypothermia. The pupils were sluggish but equally reactive to light, and findings on funduscopic examination were normal. The neck was supple and there were no meningeal signs. The lungs were clear to auscultation and percussion. The pulses were decreased but present in all four extremities. Examination of the precordium disclosed a normal point of maximum impulse (PMI) and a grade 2 (on a scale of 6) systolic ejection murmur at the lower left sternal border. No rubs or gallops were noted. There was minimal tenderness of the abdomen over the upper quadrants. The liver was 10.0 cm by percussion and there were no masses or splenomegaly. Neurological examination showed garbled, slurred speech, and decreased gag and cough reflex. Cranial nerves II through XII were otherwise intact. The deep tendon reflexes were absent in the lower extremities and were symmetrically equal in the upper extremities with a delayed relaxation phase. The toes were down-going bilaterally and motor strength was felt to be equal in all four extremities. The remainder of the physical examination was unremarkable, except for the odor of alcohol on her breath.

Initial Laboratory Studies

Results of laboratory studies done in the emergency room were as follows: sodium 136, chloride 102, potassium 4.8 and bicarbonate 1.0 mEq per liter; blood urea nitrogen (BUN) 12, creatinine 1.0 and glucose 86 mg per dl; serum aspartate aminotransferase (SGOT; formerly known as serum glutamic-oxaloacetic transaminase) 235 IU per liter, serum alanine aminotransferase (SGPT; formerly known as serum glutamic-pyruvic transaminase) 38 IU per liter and amylase 562 IU per liter (normal less than 81); lipase 36 IU per dl (normal less than 24); phosphorus 6.5 mg per dl; osmolality 298 mOsm; leukocyte count 19,200 cells per cu mm, with a left shift, hemoglobin 14.5 grams per dl and mean corpuscular volume (MCV) 117. Analysis of urine showed proteinuria (4+), ketonuria (2+) and microscopic hematuria. Arterial blood gas studies obtained on room air and corrected for a core temperature of 30.5°C (87.0°F)[7] were as follows: oxygen pressure (P_{O_2}) 91 mm of mercury and carbon dioxide pressure (P_{CO_2}) 13 mm of mercury; bicarbonate 1.5 mEq per liter, and pH 6.67. The arterial blood gas measurements were rechecked and the results were confirmed. An electrocardiogram disclosed normal sinus rhythm and no acute changes. There was no ectopy and no J wave present. A roentgenogram of the chest showed a small superior segmental infiltrate of the right lower lobe, but no other abnormalities. After 100 mEq of sodium bicarbonate had been given parenterally and 1.5 liters of 5 percent dextrose and normal saline infused, a repeat arterial blood gas measurement corrected for a core temperature of 31.1°C (88.0°F)[7] showed a pH of 6.75.

Hospital Course and Treatment

A central venous pressure line was placed and measured 0 cm of water pressure. An arterial femoral line showed a core blood pressure of 88/40 mm of mercury. A Swan-Ganz line was placed a few hours later while the patient was in the intensive care unit. A nasogastric tube detected heme-positive material but no active bleeding. A lumbar puncture yielded normal cerebrospinal fluid on microscopic examination.

The patient was treated vigorously with intravenous fluid replacement consisting of 5 percent dextrose with normal saline and plasmanate (approximately 10 liters in 24 hours). Thiamine was given parenterally. She was given 600 mEq of sodium bicarbonate in 24 hours (12 ampuls with 50 mEq of sodium bicarbonate per ampul). Broad-spectrum antibiotic drugs and 1 gram of methylprednisolone sodium succinate (Solu-Medrol) were administered for suspected Gram-negative sepsis; 500 μg of sodium levothyroxine (Synthroid) was given intravenously for suspected myxedematous coma. A heating blanket was used and the patient's temperature was monitored continuously by rectal probe thermometer. The core rectal temperature increased by approximately 0.6°C per hour until it reached 37.0°C (98.6°F) within 12 hours after admission. The pH was corrected more slowly to a pH of greater than 7.25 during the second 24 hours

with the use of 400 mEq of sodium bicarbonate (8 ampuls of sodium bicarbonate). The pH continued to increase, to a level of greater than 7.55 after 48 hours of admission. The hypovolemia and hypotension were corrected with vigorous fluid management which included maximizing the wedge pressure and cardiac output. At no time was the patient oliguric. After hydration the hemoglobin diluted from 14.5 to 11.7 grams per dl. The patient's weight increased from 66 to 71.7 kg.

The elevated anion gap resolved within 72 hours. The studies of the elevated anion gap showed an arterial blood level of lactate to be 180 mg per dl, and pyruvate to be 0.5 mg per dl. Methanol, paraldehyde, ethylene glycol and salicylate levels were all negative. Serum ketones were positive at 1:4 dilution and serum osmolality was 298 mOsm. The alcohol level was 0.07 gram per dl. The lactate level decreased from 180 to 63 mg per dl within 24 hours of admission.

The random serum glucose level rose from 86 to 824 mg per dl within 24 hours of admission and ketones increased from 1:4 to 1:8 dilution. The diabetic ketoacidosis was managed with continuous infusion of low doses of insulin. The phosphorus level, which was originally 6.5 mg per dl (rechecked and confirmed) fell to less than 0.2 mg per dl after insulin infusion was begun for the hyperglycemic ketosis. This condition was successfully treated with potassium phosphate.

Serum amylase levels remained elevated and the amylase to creatinine clearance ratio obtained 24 hours after admission was greater than 10 percent. Intermittent nasogastric suctioning and intravenous hydration eventually led to resolution of the abdominal pain and return of amylase levels to normal.

Other causes for hypothermia that were ruled out included a coma panel which was negative for barbiturates and phenothiazines. Thyroid function studies obtained on admission showed a normal thyroid-stimulating hormone level (TSH) and a borderline normal free thyroxine index (T7). Pituitary and adrenal functions were deemed adequate on the basis of normal gonadotropin levels and a normal response to a metapyrone suppression test with appropriate elevation of 11-deoxycortisol (compound S).

Follow-up cultures of the blood, urine and cerebrospinal fluid (CSF) obtained on admission were all negative and antibiotic therapy was eventually discontinued. During the first few days after admission, there were evolutionary changes in the patient's EKG consistent with the diagnosis of subendocardial myocardial infarction; cardiac isoenzyme series for creatine phosphokinase (CPK) were also diagnostic for a myocardial infarction. However, the patient tolerated this infarction without any complications. The patient was discharged on the 15th hospital day in her usual state of health, euthermic, with a normal amylase and serum glucose levels. A repeat roentgenogram of the chest showed resolution of the previously noted infiltrate.

Discussion

The patient was admitted to hospital with a severe metabolic acidosis involving an anion gap of greater than 30. The severity of the acidosis and the subsequent survival of this patient are unique—to my knowledge there are no other such cases reported in the literature. The patient's survival appears to be, in part, a result of concomitant hypothermia which had a protective effect by decreasing metabolic demands by approximately 40 percent.[8]

The differential diagnosis for metabolic acidosis with an elevated anion gap is well reviewed elsewhere.[9] Although the ketones were positive at 1:4 dilution in the blood, this was not elevated enough to explain the severity of the acidosis. The arterial lactate level of 180 mg per dl was significantly elevated (normal less than 15 mg per dl). This represented a lactate level of 20 mEq per liter with a pyruvate level of less than 0.1 mEq per liter.

The cause of the elevated lactic acidosis in this case could have been due to a combination of any of the following: hypotension and hypovolemia, alcoholism, pancreatitis, diabetes or hypothermia.[10,11] Lactic acidosis resulting from hypothermia is not common but has been noted. It is secondary to microcirculatory insufficiency coupled with the shivering reflex which produces lactic acid.[11]

The clinical features of hypothermia (core temperature of less than 35°C [95°F]) are multiple and have been recently reviewed by Reuler.[11] In this case the hypothermia was felt to be secondary to ethanol and environmental exposure. Hypothermia in the alcoholic population is not unusual.[11,12] The central nervous system depressant effects and the vasodilatory

effects coupled with environmental exposure are the common explanations for this phenomenon.

Typical physical findings of hypothermia include absence of shivering, sluggish pupils, delayed reflexes, decreased mentation, decreased cough reflex and hypotension as the hypothermia progresses.[11,12] My patient exhibited all of these findings. A decreased cough reflex and cold-induced bronchorrhea often lead to aspiration pneumonia, which may have been present in this patient as she had a common segmental lobe involvement for aspiration when supine.

The hypovolemia could be attributed to the three-day history of vomiting, but this should have generated some bicarbonate, and the degree of metabolic acidosis should not have been as severe. Another explanation for the hypovolemia is cold diuresis.[11,13] The normal hemoglobin on admission in this patient with documented folate-deficiency anemia was probably secondary to hemoconcentration and splenic contracture seen in hypothermia.[11] Gastric submucosal hemorrhage is also common in hypothermia and may have accounted for the heme-positive nasogastric aspirate and for a portion of the subsequent drop in hemoglobin.[11]

The diagnosis of pancreatitis was supported by the symptoms, physical findings and an elevated amylase to creatinine clearance ratio of greater than 10 percent.[14] The cause of pancreatitis may have been alcohol abuse, but this condition has also been reported with hypothermia.[15,16] Furthermore, diabetic ketoacidosis in conjunction with acute pancreatitis, secondary to accidental hypothermia, is recognized.[17] The mechanism for diabetes mellitus with hypothermia is secondary to inhibition of insulin release[18] and decreased effectiveness of insulin, along with the pancreatitis itself.[17] It should be noted that hyperamylasemia and an elevated amylase to creatinine clearance ratio is not specific for the diagnosis of pancreatitis in the presence of diabetic ketoacidosis.[14,19] However, with the ratio of greater than 10 percent, it is likely that the pancreas was the source of the elevated levels of serum amylase.

The possibility that hypothermia develops as a consequence of diabetic ketoacidosis has also been suggested.[4] However, in these cases severe hyperglycemic-ketotic, hyperosmolar states are described. In this patient, the initial serum glucose value of 86 mg per dl rules out this possibility. The diabetic ketoacidosis, which in fact ensued hours after admission, was partially induced by the generous amounts of parenteral glucose infused in a hypothermic state[20] in which peripheral utilization of glucose was reduced. The rising ketonemia after starting the infusion of low doses of insulin undoubtedly reflected an improved oxidative state and consequent metabolism of β-hydroxybutyrate.[21]

The elevated level of phosphorus noted on admission has previously been described in cases of severe lactic acidosis.[3] The precipitous drop of serum phosphorus to 0.2 mg per dl could be attributed to the treatment phase of diabetic ketoacidosis, but it has also recently been observed to occur as a complication of the rewarming phase in hypothermia.[22] The methods available for rewarming hypothermic patients are by peripheral warming techniques and by internal methods.[23] The patient in this case tolerated the slow rewarming by peripheral means without difficulty. There was no observed drop in core temperature using the peripheral warming technique as has sometimes been described.[23]

Summary

A case of severe lactic acidosis with hypothermia is described. Survival of a patient with this degree of lactic acidosis is unique and, undoubtedly, was secondary to decreased metabolic demands present in a state of hypothermia. The cause of the lactic acidosis may have been secondary to the hypothermia alone. The patient was felt to be hypothermic as a result of environmental exposure in conjunction with an alcoholic state. The hypothermia could account for the clinical course of this patient, which included coma, aspiration pneumonia, hypovolemia, gastric submucosa hemorrhage, pancreatitis, transient hyperglycemic ketosis and hypophosphatemia. Management of the patient's condition with bicarbonate, fluids and peripheral warming techniques is briefly discussed.

REFERENCES

1. Peretz DI, McGregor M, Dossetor JB: Lactic acidosis: A clinically significant aspect of shock. Canad Med Assoc J 90:673, 1964

2. Peretz DI, Scott HM, Duff J, et al: The significance of lactic-acidemia in the shock syndrome. Ann NY Acad Sci 119:1133-1139, 1965

3. Tranquada RE, Grant WJ, Peterson CR: Lactic acidosis. Arch Intern Med 117:192-202, 1966

4. Gale EAM, Tattersall RB: Hypothermia: A complication of diabetic ketoacidosis. Br Med J 2:1387-1389, 1978

5. Garella S, Dana CL, Chazan JA: Severity of metabolic acidosis as a determinant of bicarbonate requirements. N Engl J Med 289:121-126, 1973

6. Fulop M, Hoberman HD: Phenformin-associated metabolic acidosis. Diabetes 25:292-296, 1976

7. Kelman GR, Nunn JF: Nomograms for correction of blood PO_2, PCO_2, pH, and base excess for time and temperature. J Appl Physiol 21:1484-1490, 1966

8. Blair E: Clinical Hypothermia. New York, McGraw-Hill Co, 1964

9. Emmett M, Narins RG: Clinical use of the anion gap. Medicine 56:38-55, 1977

10. Oliva PG: Lactic acidosis. Am J Med 48:209-225, 1970

11. Reuler JB: Hypothermia: Pathophysiology, clinical settings, and management. Ann Intern Med 89:519-527, 1978

12. Weyman AE, Greenbaum DM, Grace WJ: Accidental hypothermia in an alcoholic population. Am J Med 56:13-21, 1974

13. Moyer JH, Morris G, DeBakey ME: Hypothermia: I. Effect on renal hemodynamics and on excretion of water and electrolytes in dog and man. Ann Surg 145:26-40, 1957

14. Levitt MD: Clinical use of amylase clearance and isoamylase measurements. Mayo Clin Proc 54:428-431, 1979

15. Duguid H, Simpson RG, Stowers JM: Accidental hypothermia. Lancet 2:1213-1219, 1961

16. Read AE, Emslie-Smith D, Gough KR, et al: Pancreatitis and accidental hypothermia. Lancet 2:1219-1221, 1961

17. MacLean D, Murison J, Griffiths PD: Acute pancreatitis and diabetic ketoacidosis in accidental hypothermia and hypothermic myxoedema. Br Med J 4:757-761, 1973

18. Currey DL, Curry KP: Hypothermia and insulin secretion. Endocrinology 87:750-755, 1970

19. Vinicor F, Lehrner LM, Karn RC, et al: Hyperamylasemia in diabetic ketoacidosis: Sources and significance. Ann Intern Med 91:200-204, 1979

20. Wynn V: Electrolyte disturbances associated with failure to metabolise glucose during hypothermia. Lancet 2:575-578, 1954

21. Kreisberg RA: Diabetic ketoacidosis: New concepts and trends in pathogenesis and treatment. Ann Intern Med 88:681-695, 1978

22. Levy LA: Severe hypophosphatemia as a complication of the treatment of hypothermia. Arch Intern Med 140:128-129, 1980

23. Myers RAM, Britten JS, Cowley RA: Hypothermia: Quantitative aspects of therapy. JACEP 8:523-527, 1979

Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

Treatment for Heatstroke Victims

TO THE EDITOR: This is a further comment on thermal resuscitation of heatstroke victims (Elliston E: West J Med 133:255-256, Sep 1980).

Evaporative cooling has been shown to be highly effective and probably safer than whole body emersion in the emergency room treatment of hyperthermia.[1] However, initial cooling for heatstroke or hyperthermia must begin in the field and continue during transport under conditions where optimum use of evaporative cooling may be difficult to achieve.

Cold packs applied to areas of large superficial vessels (neck, axillary, inguinal) have been used successfully to treat heatstroke in distance runners. Recent case reports have shown body cooling from initial rectal temperatures from between 43° and 42°C (109.4° and 107.6°F) to between 39.5° and 39.0°C (103.1° and 102.2°F) in 20 to 30 minutes.[2,3] This method has the advantage of immediate application and minimum cutaneous vasoconstriction.

Emergency medical crews should be instructed in rapid initiation of regional cooling for heatstroke victims using commercially available chemical cold packs.

PETER G. HANSON, MD
Associate Professor of Medicine
Center for the Health Sciences
University of Wisconsin—Madison

REFERENCES

1. Weiner JS, Khogali M: A physiological body cooling unit for treatment of heatstroke. Lancet 1:507-509, Mar 8, 1980
2. Hanson PG, Zimmerman SW: Exertional heatstroke in novice runners. JAMA 242:154-157, 1979
3. Richards D, Richards R, et al: Management of heat exhaustion in Sydney's "The Sun City-to-Surf" fun runners. Med J Aust Nov 13, 1979, pp 457-461

Tonsillectomy and Adenoidectomy

TO THE EDITOR: Several points come to mind after reading the article by Davidson and Calloway concerning tonsillectomy and adenoidectomy in the November 1980 issue.[1]

- Any physician who is caring regularly for a patient and who allows the patient to progress to right ventricular failure due to correctable upper airway obstruction, in my opinion could be guilty of criminal negligence.
- The streptococcus is not the only organism that causes tonsillitis, and cultures that only identify or exclude this organism may miss many bacterial infections.
- No mention was made in the article of chronic tonsillitis, the day-in and day-out chronic inflammation and infection of the tonsils. Chronic tonsillitis may well represent the only chronic infectious disease in the body, relatively easily corrected by a surgical procedure, that is accepted as a normal state.

GORDON BREITMAN, MD
Glendale, California

REFERENCE

1. Davidson TM, Calloway CA: Tonsillectomy and adenoidectomy—Its indications and its problems (Information). West J Med 133:451-454 Nov 1980

Radiation Therapy for Skin Cancer

TO THE EDITOR: In the November issue, Fischbach and colleagues state their case for the radiation therapy of skin cancer.[1] Unfortunately, their study and, therefore, their conclusions are marred by their woefully short follow-up. The authors do not provide data as to the length of follow-up except to state that there was a minimum two-year follow-up period, and "for most the period of evaluation was longer." Since the study was begun in 1969, and the paper published in 1980, ten years was the maximum follow-up—and for most it was obviously less.

The authors fail to recognize that any short-term conclusions regarding the results of radiotherapy of the skin are bound to be wrong. Numerous observations have shown that significant skin radiation—well below the doses used in radiotherapy of skin cancer—tends to result in carcinomatous degeneration decades later. Radiation scars are notorious for *late* recurrences or carcinomatous degeneration—it is often impossible to decide which mechanism is responsible.

Similarly, Fischbach's conclusions that "cosmetic and functional results were excellent" is

meaningless. Unlike surgical scars, which remain stationary or improve with time, radiation scars worsen with time. This is not just a cosmetic nuisance, but the gradually deteriorating appearance of a radiation scar often masks recurrent carcinoma within it.

It puzzles me why after 50 years of documentation of the insidious late effect of radiation on the skin, the short-term results of radiation therapy for skin cancer would be published. There are plenty of studies documenting the good *short-term* results of fractionated radiotherapy.

Most dermatologists avoid radiotherapy for skin cancer; we have seen too many bad late results. Possibly the more modern techniques of increased fractionation of the radiation dose—as used by Dr. Fischbach and associates—will provide better long-term results. The burden of proof is on those advocating radiotherapy; they must show that it is possible to dissociate the short-term good therapeutic results from the long-term complications of skin radiation. Until this proof is forthcoming, I believe radiotherapy of skin cancer should be limited to the very few patients who are unable to tolerate, or who refuse, surgical removal.

ERNST EPSTEIN, MD
San Mateo, California

REFERENCE

1. Fischbach AJ, Sause WT, Plenk HP: Radiation therapy for skin cancer. West J Med 133:379-382, Nov 1980

Possible Hazards of Nylon Athletic Shorts

To the Editor: Nylon athletic shorts have become increasingly popular; recently, built-in nylon underwear has been added to this type of shorts. I have seen at least two cases of significant problems caused by nylon athletic shorts with built-in underwear. In the first instance, a patient, due to the poor insulating qualities of the nylon athletic shorts, developed penile frostbite during a 40-minute run in foggy 40°F weather; this resolved with warming of the involved part in 100°F water for 15 to 20 minutes. In the second instance, a patient presented with symptoms of urethritis. A workup was done for this diagnosis before it was found that he was a weight lifter who had recently switched to nylon athletic shorts; it was discovered that the urethral meatus was being irritated by the chafing of the nylon. It seems that wearing an athletic supporter or cotton underwear under nylon running shorts would be prudent; this would decrease chafing and increase insulation. It likewise seems that fungal groin rashes would be more likely to occur where nylon running shorts frequently are worn alone.

ED SARGENT, MD
Student Health Center
Oregon State University
Corvallis, OR

REFERENCES

1. Hershkowitz M: Penile frostbite, an unforeseen hazard of jogging. N Engl J Med 296:178, 1977
2. Levit F: Jogger's nipples. N Engl J Med 297:1127, 1977
3. Deutsch M: Jogger's ailments. N Engl Med 298:405, 1978
4. Newuin, N: Jogger's ailments. N Engl J Med 298:405-406, 1978

TdT Negative T-ALL

To the Editor: T acute lymphocytic leukemia (T-ALL) makes up about 30 percent of all cases of acute leukemia and can be characterized by the blasts which have the ability to form E rosettes, demonstrate the theta antigen and contain the enzyme terminal deoxynucleotidyl transferase (TdT).[1] The use of the TdT assays has been found to be extremely useful in distinguishing acute lymphocytic leukemia (ALL) from acute myelogenous leukemia (AML), or—more important—prednisone-vincristine responsive acute leukemia. Recently Saab and Carloss reported a case of lymphoblastic leukemia without TdT.[2] We wish to report here the case of a patient with acute lymphocytic leukemia in whom the blasts were E rosette-positive and theta antigen-positive but in whom TdT was absent.

Report of a Case

A 62-year-old woman presented with a leukocyte count of 44,000 per cu mm, anemia, thrombocytopenia and uric acid nephropathy. The leukocyte count rose within 48 hours to 169,000 per cu mm and uremia supervened (uric acid peaked at 43 mg per dl). Hemodialysis and allopurinol therapy resulted in a reversal of the uric acid nephropathy. Findings on a bone marrow examination confirmed ALL. Once the renal status stabilized, vincristine and prednisone therapy produced a remission within approximately 14 days.

The patient refused maintenance chemotherapy, and overt relapse occurred six weeks later. Again, the leukocyte count rose suddenly and precipitously to 180,000 per cu mm. Vincristine, prednisone and doxorubicin hydrochloride (Adriamycin) were given. Within 24 hours the leukocyte count dropped and hypocalcemic, hyperphosphatemic tetany supervened (calcium, 5.5 mg per dl; potas-

sium, 23 mg per dl). Appropriate therapy reversed this tumor lysis syndrome. The patient entered second remission.

About a month later the patient relapsed in spite of maintenance chemotherapy. She proved resistant to subsequent chemotherapy with cyclophosphamide, cytosine arabinoside, vincristine, prednisone and l-asparaginase, although the aggressive proliferative aspects of the leukemia to date have been controlled by this therapy.

The blasts on Wright-Giemsa morphology ranged from small L-1 types with a high nuclear cytoplasmic ratio, mature chromatin and indistinct nucleoli, to forms that almost approached mature lymphocytes. Cytochemical stains for AML (Sudan, peroxidase and chloracetate esterase) were negative. Periodic acid-Schiff (PAS) stain was negative for block positivity. Lipase stain showed punctate positivity in some forms, which is a characteristic seen with some cases of ALL. Terminal deoxynucleotidyl transferase by immunofluorescent method was negative twice, and by the biochemical method done twice on both blood and bone marrow (at City of Hope National Medical Center, Los Angeles) also negative—in a blood specimen on January 2, the protein value was 1.1 μU per mg (normal less than 5.2 μU per mg); in a blood specimen on April 2, the protein value was 4.0 μU per mg and in a bone marrow specimen on April 2, there was a 7.4 μU per mg of protein value (normal less than 22.6 μU per mg). Lymphocyte marker studies were done on several occasions and showed E rosettes of 88 percent and of 82 percent, and surface immunoglobulin-bearing cells of 10 percent and 5 percent. An anti-theta antigen study using monoclonal mouse anti-sera showed 77 percent, an anti-Ia 12 percent and an anti-common ALL antigen 0 percent (last three tests carried out by Dr. Richard Gatti's laboratory, Cedars-Sinai Medical Center).

Variants of T-ALL exist. A recent report by Richie and co-workers[3] described the case of a patient with T-ALL who was anti-T positive but E rosette negative. The authors hypothesized that in their case the leukemic cells represented an early stage of T cell maturation. In our case we feel that the T cells may represent a late stage in maturation where TdT activity is lost. The mature nature of the cells may account for the immediate and dramatic response to vincristine and prednisone on two occasions. We suggest that this subset of T-ALL should be searched for to anticipate a rapid response and a tumor lysis syndrome.

STEPHEN LEE, MD
DAVID ROSENBAUM, MD
Cedars-Sinai Medical Center
Los Angeles

REFERENCES

1. Kung PC, Long JC, McCaffrey RP, et al: Terminal deoxynucleotidyl transferase in the diagnosis of leukemia and malignant lymphoma. Am J Med 64:788-794, May 1978

2. Saab GA, Carloss H: Lymphoblastic lymphoma without TdT. N Engl J Med 302:969-970, Apr 1980

3. Richie ER, Sullivan MP, van Eys J: A unique surface marker profile in T-cell acute lymphocytic leukemia. Blood 55:702-705, Apr 1980

The Importance of Making Precise Medical Records in the 1980's

TO THE EDITOR: While serving as a prosecution attorney for California's Board of Medical Quality Assurance, I noted the problems physicians had in persuading the trier of fact as to the credibility of their perception of the events or their memories of them. During the last three years, I have defended physicians before the Board, and have been involved in defense malpractice cases. It is evident to me that physicians continue to fail to realize the importance of keeping detailed medical records.

A physician may treat patients for years without much thought to his record keeping. Then one day he is sued, and he discovers that his records do not substantiate the professional decisions he made at the time. He is left to the recollection of such events, some happening many years before the lawsuit is filed. Before he finally is called to testify, additional years may intervene to cloud his memory. It then becomes a matter of credibility. A physician who sees many patients a day, over a period of years, may have a difficult time convincing anyone that he can recall, without precise medical records, how he treated one particular patient.

By carefully documenting all aspects of patient care and treatment, a physician will not be limited to his memory, should he ever be required to defend his professional decisions. Detailed record keeping should not only refresh his memory of a particular case, but also bolster his credibility in court, should a dispute arise.

Some physicians may balk at keeping detailed medical records, claiming it interferes with or takes time away from the practice of medicine. This position fails to accept the realities of practicing medicine in the 1980's. Patients expect more from physicians today than ever before. Many

patients demand perfection from their physicians. Our consumer-oriented society would seem to require that if a patient pays a physician a certain amount of money for medical treatment, the results should be "instant good health." If this is not obtained, the patient may feel he has been cheated, financially as well as medically, and may seek retribution in the courts.

Maintaining careful records need not interfere with the practice of medicine. With modern minitape recorders, no physician needs to spend hours compiling records. After conversations with each patient, he can spend a few minutes recording the pertinent information, which later can be transcribed into the patient's chart. An additional benefit of such a system is that a physician is afforded a second opportunity to determine whether the essentials are correctly recorded, and to reconsider the professional judgments he has recently made. The *recording, transcribing and proofreading* system can also assist a physician in properly monitoring and following the progress of a patient. For example, a physician may request a variety of laboratory or clinical tests to be carried out, or recommend a consultation with another physician. Because many patients may not fully understand the nature of their condition, they may not realize the importance of such tests or second opinions. By failing to follow the physician's instructions, or by postponing appointments or tests, the patient may be contributing to his own decline in health. In such cases, a review of the records gives the physician a further opportunity to recall the patient's condition, and see whether or not the patient has returned for recommended tests, and whether the results of any second opinion have been received. This reading of the transcribed notes will alert the physician to these trouble spots, and he can take steps to see that the patient is advised of the importance of following through with recommended treatment. A note can be made in the chart that the patient was contacted for this purpose.

In administering or prescribing medications, the rules of informed consent must apply. The physician must explain to the patient the purpose of the medications, and must record this information as well as the medical indications that are the basis for his decision to medicate. The patient must be informed of the possible undesirable effects of the particular drug and whether other medications or alcohol may be taken simultaneously. The patient should be told what side effects or allergic reactions should be reported to the physician. All of these elements of informed consent should be documented in the patient's chart.

Also helpful is a brief dialogue between the physician and patient, in which the physician assures himself that the patient understands the information related, whether about drugs or any other aspect of medical treatment, and whether treatment is approved by the patient or postponed by the patient. Finally, detailed records of these aspects of patient care and treatment are essential. The old saying "An ounce of prevention is worth a pound of cure" has more than one meaning in contemporary medicine. A little extra time and effort in a physician's office today may well prevent, or at least mitigate, a major calamity in the courts at some future time.

SAMUEL E. SPITAL, ESQ.
San Diego

Subacute Laetrile Intoxication

TO THE EDITOR: Laetrile, despite a federal ban and a paucity of sound evidence in the efficacious treatment of cancer, is legal in many states, most recently in California (January 1981). There are several reports[1-4] of toxicity and death due to overdose with Laetrile. However, this case presents a patient who was successfully treated for documented cyanide poisoning with Laetrile taken in "therapeutic" dosages. Laetrile's increasing acceptance by lay persons, a segment of the medical community and state legislators mandates clinical recognition of its toxicity.

Report of a Case

A 45-year-old white woman presented to the emergency department with onset over the preceding two hours of progressive dyspnea and agitation. She had had a left mastectomy in July 1978 for a documented adenocarcinoma; and a left thoracentesis had been required in November 1980 for drainage of a pleural effusion caused by the malignancy. A bone scan done during that hospital stay showed positive isotope uptake in multiple anterior ribs. The patient's medications on present admission included vitamin A (once daily), yeast, multivitamins (once daily), occasional aspirin tablets for rib pain, tamoxifen (10 mg orally twice a day) and Laetrile (10 ml injections [3 grams] intravenously, three times a week and 1 gram orally, twice a day, on the days which she was not receiving it intravenously). The

patient had last taken Laetrile, orally, the previous night, 12 hours before admission. She had been taking the drug in this dosage regimen for about a month since the thoracentesis. One year previously she had completed a ten-month course of Laetrile. The more recent supply was apparently obtained from Italy, instead of Mexico, the source of her first course.

On physical examination the patient was agitated, clutched her chest and was in apparent respiratory distress. The vital signs were blood pressure 170/85, right arm recumbent, pulse of 116 and regular, respiratory rate of 30 and labored, and oral temperature of 37.4°C. The patient had a peculiar acrid odor to her breath, unrecognizable to several observers. There was no jugular venous distention, nor carotid bruits. The left breast was surgically absent and the right breast without masses or scars. Other than some tachycardia, the results of cardiac examination were within normal limits. There was dullness to percussion over the entire left lung field with slight tracheal deviation to the right. The right lung was normal to auscultation and percussion. The skin was of normal color, and the remainder of the physical examination gave findings within normal limits.

Laboratory studies carried out on admission gave the following values: arterial oxygen pressure (PaO_2) 69 torr (fraction of inspired oxygen [FIO_2] 0.21), arterial carbon dioxide pressure ($PaCO_2$) 31 torr, pH 6.97, bicarbonate 7 mEq per liter and acetone determination was negative. The lactate level was 18.7 mEq per liter (normal 0.5 to 2.2) and the salicylate level was 11.6 mg per dl (therapeutic 2 to 29). The routine toxicologic screen was negative. Findings on serum electrolyte studies, liver function tests, determinations of serum blood urea nitrogen and serum creatinine, and complete blood count were all within normal limits. Repeat arterial blood gas determinations confirmed a severe partially-compensated metabolic acidosis with a calculated anion gap of 24. Cyanide levels showed a serum value of 0.5 μg per ml and a blood value of 1.1 μg per ml (toxic >0.3; lethal >1.0).

Oxygen was administered at 10 liters per minute through nasal cannulae, and 1 amp (44.5 mEq) of sodium bicarbonate was administered intravenously. Gastric lavage was started and the patient was transferred to the coronary care unit where she became more unresponsive. Her respiratory rate fell to eight per minute and was labored requiring endotracheal intubation. Electrocardiographic monitoring which previously had shown a sinus rhythm without ectopy, showed a sinus bradycardia at a rate of 38 with multiple unifocal ventricular contractions.

As the cyanide antidote was being prepared for injection, the patient sustained a 20-second generalized tonic-clonic seizure. A pearl of amyl nitrite was crushed and held in a gauze pad at the patient's open endotracheal tube for 20 seconds. Next, 10 ml of 3 percent sodium nitrite solution (0.3 gram) was injected intravenously followed immediately by 50 ml of 25 percent sodium thiosulfate solution through the same needle. The patient's cardiac and respiratory status stabilized, and she was extubated five hours after admission after a normal set of arterial blood gas values was obtained. On the second hospital day the patient, who was now without signs or symptoms of cyanide toxicity, was transferred to the ward. She was able to walk and drink fluids. After a diagnostic and therapeutic thoracentesis the patient was discharged on the fourth hospital day.

Discussion

Previous reports of Laetrile's toxic effects have often failed to document potentially lethal levels of cyanide at the time of admission.[3-5] To our knowledge, a case of Laetrile toxicity has not been reported in which the patient was taking the drug in the manner and dosage prescribed.

Cyanide inhibits oxidative phosphorylation at the cytochrome oxidase level within the mitochondrion. Cyanate combines with the a3 complex and prevents oxygen from reoxidizing previously reduced cytochrome a3. Thus, in a rapid fashion electron transport, mitochondrial oxygen utilization and cellular respiration are inhibited.[12] Clinically, these biochemical derangements evoke increased lactic acid production and lactic acidosis with a concomitant fall in serum bicarbonate, abolition of arteriovenous oxygen differences (venous blood appears bright red) and increased brain lactate levels and decreased AIP levels

Items submitted for the Correspondence section should be typed double-spaced (including references) with conventional margins. The text should not exceed 600 words.

(diminished levels of consciousness).[5] The diagnosis of cyanide poisoning has a few specific physical findings for its support. The bitter almond breath odor is detected by 25 percent to 80 percent of physician *sniffers*.[5,6] Abolition of the arteriovenous oxygen difference manifested by an equal red appearance in arterial and venous blood[15] is not a consistent finding and was not found in the present case. Pulmonary edema and lactic acidosis have been reported,[5] but are nonspecific as are the other clinical manifestations of cyanide poisoning.

This case demonstrates the possibility of different cyanogenic potential from Laetrile of different origin. Significant differences in biochemical and physiochemical properties have been found in Laetrile distributed for clinical trials in the United States and Canada.[9]

The treatment of cyanide poisoning is well covered elsewhere.[10,11] The cyanide treatment kit (Lilly) is the current standard in the United States. The kit utilizes amyl nitrate and sodium nitrite to oxidize hemoglobin to methemoglobin. The methemoglobin binds cyanate, forming cyanmethemoglobin, which in the presence of thiosulfate, dissociates into thiocyanate and sodium sulfate. Thiocyanate, relatively nontoxic, is easily eliminated by the kidneys.

Summary

A 45-year-old woman taking "therapeutic" dosages of a Laetrile compound was treated successfully after presenting with signs and symptoms of cyanide toxicity. Because of the trend toward legalization of Laetrile and its sanction in many states, subacute and more familiar acute poisoning deserve closer clinical scrutiny.

RICHARD C. BARNETT, MD
JAMES POINTER, MD
JOHN NIMTZ, MD
RICHARD BEERS, MD
Community Hospital
Santa Rosa, California

REFERENCES

1. Ortega JA, Creek JE: Acute cyanide poisoning following administration of Laetrile enemas. J Pediatr 95:1059, Dec 1978

2. Morse DL, Bo L, Findley PA: More on cyanide poisoning from Laetrile. N Engl J Med 301:892, Oct 18, 1979

3. Sadoff L, Fuchs K, Hollander J: Rapid death associated with Laetrile ingestion. JAMA 239:1552, Apr 14, 1978

4. Braico KT, Humbert JR, Terplan KL, et al: Laetrile intoxication—Report of a fatal case. N Engl J Med 300:238-240, Feb 1, 1979

5. Graham DL, Laman D, Theodore J, et al: Acute cyanide poisoning complicated by lactic acidosis and pulmonary edema. Arch Intern Med 137:1051-1055, Aug 1977

6. Arena J: Cyanide, chap 4.14, *In* Tintinalli J (Ed): Study Guide in Emergency Medicine. Dallas, American College of Emergency Physicians, 1978, pp 4-71 - 4-74

7. Berlin CM: The treatment of cyanide poisoning in children. Pediatrics 46:793-796, Nov 1970

8. Buchanan IS, Dhamee MS, Griffiths FE, et al: Abnormal fundal appearances in a case of poisoning by a cyanide capsule. Med Sci Law 16:29-36, 1976

9. Levi L, French WN: Laetrile: A study of its physiochemical and biochemical properties. Can Med Assoc J 92:1057-1061, May 15, 1965

10. Chen KK, Rose CL: Treatment of acute cyanide poisoning. JAMA 162:1154-1155, Nov 17, 1956

11. Ivankovich AD, Braverman V: Cyanide antidotes and methods of their administration in dogs. Anesthesiology 52:210-216, Mar 1980

Private Enterprise Physicians, An Endangered Species?

To the Editor: Private enterprise physicians might be an endangered species. If current attacks continue, the United States judiciary may soon read the last rites over our once august body. Just now we are particularly vulnerable because the medical profession has been concentrating on the *science* of medicine more than the *art* of medicine, that which incorporates activity of the right hemisphere of the brain—daring, imagination and persuasive communication.[1]

Our ancient predecessors who practiced the *sacred art* of medicine spoke and wrote persuasively in defense of their profession, fully supported by oratory, logical argument and effective rhetoric. Nearly destroyed for a time by the early Christian church, medicine was revived by physicians who called upon art, daring and innovation to overcome their profession's enemies.[2] Sometimes defying the penalty of death, they dissected cadavers and learned—gradually triumphing over the forces of superstition and unreason.

Today our adversaries are as clearly discernible and dangerous as those our ancestors defeated earlier, but do we possess the tools—the heart, daring and oratorical skills—to save our profession for future generations? Our opponents, politicians, many of them lawyers, are well versed in oratory and can use their skills to persuade with evangelical effect. Though law is a heavily left-hemisphere activity, and law dominates all branches of our government, the forces that mold men's minds often emanate from the right hemisphere.[1] Should not we, too, private medicine, develop and nurture the seeds of our salvation? Instead of becoming more left-hemispheric[1] (scientific) and ingrown, thus contributing to our own destruction, we should improve our persuasive skills and counter-attack those who would legislate us out of existence.

The judiciary and clergy (mostly good people) who are destroying private enterprise medicine

think they are benefiting our patients and us as well. But, as in earlier times when the clergy burned people at the stake to save their souls, their medicine is killing the patient: paper work inundates us, malpractice suits assail us, and cost-effectiveness experts castigate us. Faced with increasing regulations, mounting insurance premiums, rising public criticism and moves toward socialization, physicians are leaving this profession, and bright students are entering others.

What can we do to staunch this loss of our life's blood? Our main defense lies in our patients. When they are pleased with our performance we are less vulnerable. Unfortunately, one problem we face is the patient's notion that doctors are omniscient and omnipotent, a harmfully erroneous attitude. As one lawyer remarked, "Patients think of doctors as junior gods, but since people don't understand God, they don't understand doctors either." Let us help our patient-employers understand us better. To do this we must descend from the pedestal they have placed us on. We must let them know our humanity, our shared concerns, what we can and cannot do.

We can also publicize the virtues of our profession. Medicine is both *logical* and *moral*. Unlike the legal profession, which is logical and amoral (legalizing tobacco) and the clerical profession, which is moral but illogical (opposing all abortion, all euthanasia), the medical profession stands as a corrective, judicious balance between law's critical, analytical left-hemisphere mode and religion's emotional, intuitive right-hemisphere mode. Whereas both left-mode and right-mode strive for *perfection* (the enemy of good), the balanced mid-mode, by adhering to a standard and allocating functions to whichever hemisphere does it best, strives toward *good*. (Interestingly, the judiciary, the clergy and the villainous Darth Vader wear black; the medical profession, the nursing profession and the heroic Luke Skywalker wear white.) Medicine's role, then, is to care for the real physical and psychological needs of mankind. We are neither paid to marshal arguments for legislation in this life or prepare souls for the next. We are simply concerned with what is knowably true and good. I suggest that we need to communicate this more clearly.

So we must learn to speak and write more persuasively. To this end, including a Dale Carnegie type course in public speaking and effective communication[3,4] in the medical school curriculum, and for practitioners as well, might help us compete with lawyers and clergymen who are trained in persuasion. *We must develop all the tools necessary to protect our position as the guardians of people's health.* By balancing art and science, morality and logic, humanism and research, we can not only benefit our patients, but also help preserve the life of the medical profession our ancestors fought so valiantly to revive and bequeath to us.

JOHN M. DOUGLASS, MD
Coordinator of Health Improvement Service
Kaiser-Permanente Medical Center
Los Angeles

REFERENCES

1. Edwards B: Drawing on the Right Side of the Brain. Los Angeles, JP Tarcher Inc, 26-40, 1979
2. Major RH: A History of Medicine. Springfield, IL, Charles C Thomas, 207-478, 1954
3. Carnegie D: The Quick and Easy Way to Effective Speaking. Garden City, Dale Carnegie & Associates, Inc, 1962
4. Carnegie D: How to Win Friends and Influence People. New York, Simon and Schuster, 1964

High Altitude Flatus Expulsion (HAFE)

TO THE EDITOR: We would like to report our observations upon a new gastrointestinal syndrome, which we shall refer to by the acronym HAFE (high altitude flatus expulsion). This phenomenon was most recently witnessed by us during an expedition in the San Juan Mountains of southwestern Colorado, with similar experiences during excursions past. The syndrome is strictly associated with ascent, and is characterized by an increase in both the volume and the frequency of the passage of flatus, which spontaneously occurs while climbing to altitudes of 11,000 feet or greater. The eructations (known to veteran back-packers as "Rocky Mountain barking spiders") do not appear to vary with exercise, but may well be closely linked to diet.[1] The fact that the syndrome invariably abated on descent leads us to postulate a mechanism whereby the victim is afflicted by the expansion of colonic gas at the decreased atmospheric pressure of high altitude. This is somewhat analogous to the rapid intravascular expansion of nitrogen which afflicts deep-sea divers and triggers decompression illness.

While not as catastrophic as barotrauma nor as debilitating as HAPE (high altitude pulmonary edema), HAFE nonetheless represents a significant inconvenience to those who prefer to hike in company. Some experience from recent Everest expeditions suggests that the use of digestive enzymes and simethicone may minimize the hazard.

At present, we can advise victims that the offense is more sociologic than physiologic.

HAFE should be added to the growing list of medical disorders that are associated with exposure to high altitude. We are planning a prospective study for the summer of 1981.

PAUL AUERBACH, MD
Assistant Professor of Medicine
Attending Physician, Emergency Services
Temple University Hospital
Philadelphia

YORK E. MILLER, MD
Research Fellow
Pulmonary Division
Department of Medicine
University of Colorado Health Sciences Center
Denver

REFERENCE

1. Levitt MD, Lasser RB, Schwartz JS, et al: Studies of a flatulent patient. N Engl J Med 295:260-262, Jul 29, 1976

Medicaid and the Medical Profession

TO THE EDITOR: It would be unfortunate for the medical profession to view Medicaid as a "dismal failure" (Meyerowitz BR: Medi-Cal: A Debacle? West J Med 133:449-450, Nov 1980). When Congress enacted Medicare in 1965, it tacked on the American Medical Association's Eldercare proposal but spelled out its benefits to those who were "medically indigent" and called it Medicaid. This was the *sleeper clause* that some saw as the real troublemaker for the country and medical profession because of the experience with the Kerr-Mills program (*Chicago Tribune,* August 20, 1966). The same basic premise, medical indigence, underlay the old Kerr-Mills program which applied only to the aged. This program was actively and passively opposed by those who disliked its means test (calling it a "pauper's oath," which it decidedly was not) and who were committed to the all or none principle of coverage for benefits. Various obstacles were used to prevent its smooth operation where enacted and in many states even its initiation was blocked. The same ideologic forces, intent upon a total federal program, are lined up against Medicaid.

In 1965 there were those who actually believed that those concrete forests of old-fashioned public *charity,* the municipal hospitals, would close their doors "because Medicare and Medicaid should do away with the need for hospitals that take care of the indigent." Dr. Meyerowitz and the rest of us know better today. We have not forgotten the promises that physicians would not have to donate their services to charitable purposes; we recognize them as the usual inducements to encourage less opposition to proposed legislative medical measures.

The derogatory portrayal of Medicaid ought to act as a catalyst to a dogged perseverance in our attack on the opposition through repeated emphasis on the benefits of Medicaid. It would seem proper to emphasize that Medicaid has had an effect for the better on the delivery of health services to the poor. Some improvements are necessary, but let us not dump the program and join the opposition. Some progress towards a one-class system of medical care was made in the 15 years of existence of Medicaid. But the zeal for such a result should be tempered by the recognition that even in England the effort is failing significantly.

There is some recent indication of encouragement with the use of computerized management systems in Medicaid administration. Furthermore, suggestions to increase Medicaid reimbursement and reduce payment delays would aid "to integrate the poor into mainstream medicine" (*American Medical News,* December 5, 1980).

The criticism that most of Medicaid expenditures go to the elderly and disabled (Medicare beneficiaries) substantiates the error of the Medicare program, which provides a little for the many (even those without the need for such subsidy) rather than enough or much for the few who really need it. Such recognition should provide the AMA with its Eldercare proposal grounds for the statement "I told you so."

And the lesson for us in the private sector? Above all, it is to continue to adhere to ethical and moral codes in our care of all patients. And we must not utilize the tactic of the opposition (the constant widespread repetition of exaggerations, half-truths and half-lies) but rather provide factual information and calm diligent disclosure of errors and misunderstandings, and of fraud and abuse. Such a program could have a constructive impact on public opinion and reinforce the current effort of those intent upon diminishing the overextended role of government in medical care provision.

EDWARD PALMER, MD
Lake Oswego, Oregon

Refer to: Chappel JN: Physician attitudes toward distressed colleagues. West J Med 134:175-180, Feb 1981

Special Article

Physician Attitudes Toward Distressed Colleagues

JOHN N. CHAPPEL, MD, *Reno, Nevada*

Attitudes and behaviors of physicians toward their impaired colleagues often affect whether the latter seek treatment. Negative responses include (1) silence, usually based on anxiety, ignorance and pessimism; (2) tentative responses based on stereotyped assumptions or distraction by organic problems; (3) judgmental responses that may result in mutual avoidance, and (4) permissive responses that encourage continued use of alcohol or other drugs. Positive responses include (1) confrontation in a concerned, constructive manner as early as possible; (2) assistance to the impaired colleague in obtaining treatment, and (3) education and information sharing to increase awareness of potential and real problems.

Educational programs can help physicians develop more positive attitudes toward both impaired colleagues and impaired patients. The emphasis is on active participation. The goals of these programs should include optimism about therapy, using structured treatment approaches that include paraprofessionals and formerly impaired physicians on the treatment team, and the development of confrontational skills on the part of each physician.

THE PROBLEM OF PHYSICIAN IMPAIRMENT is as old as the profession of medicine, but has received little mention in its history. It is only within the past decade that the problem has begun to receive systematic attention from organized medicine. The first national conference on the subject of impaired physicians, sponsored by the American Medical Association (AMA), was held in 1975. Since that time there has been increased activity in the areas of detection, discipline and treatment.

From the Department of Psychiatry and Behavioral Sciences, University of Nevada, Reno, School of Medicine.

Reprint requests to: John N. Chappel, MD, Dept. of Psychiatry and Behavioral Sciences, Anderson Medical Sciences Building, University of Nevada, Reno, NV 89557.

In the last decade the AMA has reported a sixfold increase in state disciplinary actions against physicians.[1] From 1971 to 1977 four disciplinary actions were tallied: censure, denial of license reciprocity, suspension of narcotics permits and license revocation. In 1971 there were 199 such actions arising out of 1,275 initiated. In 1977 there were 685 actions out of 3,662 initiated. These figures reflect an increase in the number and rate of disciplinary actions. Fortunately, treatment and educational options have been added to the range of disciplinary measures. The AMA model legislation prepared in 1976 adds required continuing medical education (CME),

supervision of practice, and counseling or treatment to the actions a board can take. This represents a shift toward a more positive attitude on the part of organized medicine.

Punitive discipline is usually unpleasant, and this fact contributes to avoidance of the subject of physician impairment by other physicians. It is not enough, however, to account for the variety of negative attitudes encountered among physicians. These attitudes are complex combinations of belief, emotion, knowledge and past experience. An attitude can be viewed as a learned, generalized, enduring mental readiness or predisposition to act in response to different stimuli, such as patients, family or friends.[2]

This paper reviews the literature of the relationship between attitudes and behavior of medical students and physicians and discusses early findings on physician behavior and attitudes toward their impaired colleagues. The paper concludes with some suggestions about medical education for attitudinal change.

Review of the Literature

The relationship between expressed attitudes and behavior is not clear. Research in attitudinal change shows an imprecise relationship between self-reported attitudes and behavior.[3] One of the few studies to relate attitudes to physician behavior was done by Dressler and co-workers.[4] They followed 20 residents in psychiatry who saw 248 patients admitted to the emergency room of one of Yale's teaching hospitals after attempting suicide. The residents rated each patient on a mood adjective checklist.[4] The patients whom the residents rated with warmth and understanding, indicating a positive attitude, tended to be seen for over 30 minutes and were referred as voluntary patients to private psychiatric or mental health facilities. The patients rated with disinterest and annoyance, reflecting a negative attitude, tended to be seen for less than 30 minutes and to be referred as involuntary patients to the state hospital. Clearly, other factors such as situational pressures have a major influence on behavior, and these need to be taken into account.

There is some evidence that attitudes are relatively stable over time and are not easily changed. Kiesler and colleagues have noted that "Most attitude studies show some net positive gain, but observation shows people to remain remarkably fixed in their beliefs and habitually resistant to persuasion."[3] Reynolds and Bice[5] reached a similar pessimistic conclusion after five months of vigorous efforts to alter interns' attitudes toward long-term patients whom they often labeled as "crocks."

The attitudes reflected in the negative behavior of physicians toward their impaired colleagues, as described in this paper, begin early. Rezler, in a review of attitude changes during medical school, blamed the production of "such strong feelings of inferiority in medical students that they defend themselves by becoming cynical."[6] Fisher and his colleagues documented increasingly negative attitudes toward alcoholic patients from the first year of medical school through residency training.[7]

There are some positive notes in this otherwise gloomy picture. Morse and co-workers,[8] in a survey of 665 Midwest physicians, found that the majority claimed to be comfortable with alcoholic patients, willing to make the diagnosis of alcoholism, interested in remaining medically involved during treatment, and valuing nonmedical resources such as Alcoholics Anonymous (AA). However, most also felt pessimistic about the overall outcome and recognized both the need for more education about alcoholism in medical school and their own current need for further understanding of the disease.

Educational strategies have been developed to change attitudes and to promote positive effects on physician behavior. Zimbardo and co-workers state that "all the techniques which are known to increase or decrease learning should be applicable to producing change in attitudes."[2] Jerome Frank,[9] in examining the techniques that were important in producing attitudinal change in physicians, emphasized participation, improvisation rather than rote learning, and repetition. Mogar and his colleagues[10] at Mendocino's award-winning alcoholism program (Mendocino State Hospital, Talmage, CA), have confirmed Frank's view. They believe the most powerful determinant of physician attitudes is experience working with alcoholic patients in a treatment setting which is humanistic and strongly optimistic and which tries to match the help that a patient is seeking with the kind of help the staff can provide.[10]

Physician Behavior and Attitudes

The following behavioral descriptions are based on interviews with formerly impaired physicians who have been able to resume responsible medical practice. The material summarizes the attitudes and actions of colleagues as perceived by physi-

cians who were struggling with disabling alcohol and drug abuse. (Videotapes of excerpts of these interviews are available from the author for medical educational purposes.)

Negative Behaviors

Silence is the most commonly encountered response. It is characterized by the statement, "I didn't tell and they never asked." The mutual nature of this silence on the part of the impaired physician and his or her colleagues has sometimes been referred to as collusion or conspiracy. However, there is no evidence that the silence is consciously determined. Anxiety, ignorance and pessimism all contribute to this reaction.

Anxiety may be the most common determinant. None of us want to make an unrequested diagnosis of a colleague's condition, especially when it has negative connotations and is one about which we cannot be 100 percent sure. There is also a shared anxiety about underlying anger. We fear an angry reaction and possible litigation, even though the real risk may be negligible. Our impaired colleagues fear accusations, condemnation and even "crucifixion."

Ignorance contributes in at least two ways. We are always ignorant of the full extent of the problem as experienced by a distressed colleague and, therefore, are unwilling to risk raising the issue. More important, we may be ignorant of the nature of alcohol and drug dependence, or other aspects of mental illness. Few of us received much training in these areas during our medical school, residency or continuing education experiences. Our diagnostic criteria may be stereotypic, based on skid row extremes or our own patterns of alcohol use.

Pessimism can have a powerful negative influence. Our pessimism about treatment outcome, often based on a sample of the worst cases treated in teaching hospitals, facilitates avoidance and denial. Frequently, it reflects a lack of belief both in the efficacy and outcome of treatment and in the power of peer influence or interpersonal relationships. Even greater pessimism may be felt by an impaired colleague if he believes that his condition is untreatable and that his case is hopeless.

Tentative responses are those that are partial or incomplete. These occur when we raise the issue incompletely and then let it drop. Both parties feel discomfort during the confrontation and, often, relief when the matter can be dropped. Three examples of this type of response are as follows: First, a confronting physician's stereotyped assumptions may result in the use of yes-no questions, which he or she believes will serve as a useful screening purpose. "Are you drinking a quart a week?" is a question which is easily and concretely denied by a physician who is drinking a quart a day.

Second, a confronting physician may raise the issue and then deny it himself. "You're too young to be an alcoholic," reflects an older physician's disbelief that a medical student or resident could have a problem which the physician believes occurs at an older age. This mistaken belief results in missing opportunities for early diagnosis and intervention in medical school or residency training where these problems often begin.

Distraction by other medical issues is a third example. In one case, the presence of hypertension made it possible for a resident's colleagues to ignore the young physician's alcoholism. Discomfort with emotional and behavioral problems results in avoidance behavior by attending physicians who then treat the physical effects of alcohol and drug abuse as though they were the cause. This sadly myopic pursuit of organic red herrings results in missing opportunities to obtain treatment for the underlying problem.

Judgmental responses deal with physician impairment as a moral problem rather than a medical one. The underlying tone is one of anger and condemnation. The self-righteousness implicit in this response immediately establishes a hierarchy with the impaired physician in the inferior position. "You ought to be ashamed of yourself," also has a personal quality which evokes images of childhood transgressions.

Judgmental responses are the ones most expected and feared by impaired physicians. The possibility of being blamed or condemned by an angry colleague may be used to justify not seeking help. The result is mutual avoidance between an impaired physician and his colleagues, with greatly diminished possibilities of treatment.

Permissive responses encourage others to take alcohol or drugs without regard for their potential to impair health or create dependency on their use. One physician, when applying to medical school, was interviewed in a hotel room. The young man, who was unaware of any problem at the time, informed the interviewer that he took his whiskey straight. The response was, "By God, that's the way you're supposed to drink Old Grandad!" The

ubiquitous presence of alcohol at social functions both during and after medical school, may present a persistent pressure to conform. It may also be interpreted by an insecure physician as a test of social and personal acceptability.

Less common, but more dangerous is the suggestion that alcohol or other drugs be used for the relief of tension or other symptoms. This response encourages self-prescription, which is always hazardous in that it avoids more constructive alternatives, risks increasing dependence and continues to postpone getting professional help.

Positive Behaviors

Confrontation should occur early and in a concerned, friendly, constructive way. Anger has no place in the confrontation unless the physicians involved are good friends and intend to continue their relationship. The purpose of the confrontation is to raise the issue of real or potential impairment, based on factual observation, in such a way that the physician at risk experiences support, collegial concern and optimism for treatment, if the latter is needed. It is inappropriate to attempt confrontation casually, or in passing. This response facilitates both denial and avoidance and makes the needed follow-up more difficult.

Assistance with practical issues can be very useful. Many impaired physicians who successfully get into treatment programs have received help from colleagues in making arrangements for appointments, help at home and coverage for their practice.

Education and information sharing help promote awareness of the potential for impairment in each of us and the effective help that is available. We all share the occupational hazards of our profession. It can be mutually beneficial to share our concerns and ideas with each other. Physicians should be well informed and optimistic about treatment for the causes of impairment. One such example is the Georgia Disabled Doctors Program, which has had considerable success in returning impaired physicians to successful medical practice.[11] This program emphasizes early intervention, confidentiality and voluntary participation.

Little is known about physician attitudes underlying the above behavior. Niven gave a questionnaire to 734 physicians attending CME programs at the Mayo Clinic and reported his findings at the AMA Conference on the Impaired Physician held in Minneapolis in 1977. Copies of the data can be obtained from Dr. R. G. Niven, Department of Psychiatry, Mayo Clinic, Rochester, MN 55901. The top five behaviors, rated by physicians responding to the questionnaire, as indicative of impairment problems are shown in Table 1. All of these deal with intoxication, drinking or self-prescription. Two of the five behaviors about which there was least concern included personality changes when drinking and regularly having a little too much to drink at social gatherings.

Less enthusiasm was shown on the Niven questionnaire for intervening in cases of physician impairment, as can be seen in Table 2. The notable exception was in willingness to help a physician's family and to cover his or her practice. It is this kind of assistance that greatly facilitates a physician's return to practice after treatment. Only 16 percent indicated a willingness to discuss their concern with their colleague's spouse.

We were interested in having Nevada physicians take the Niven survey for comparison purposes.

TABLE 1.—*Five Physician Behaviors Most Indicative of Problems**

Behavior	*Percent Rating Behavior as Significant (N=734)*
Is intoxicated while on call for emergency room coverage	96
Is seeing patients in his or her office after having three drinks at lunch	93
Begins to regularly use self-prescribed hypnotics, stimulants or minor tranquilizers	93
Drinks in a way that leads spouse to express serious concern that he or she has a drinking problem	93
Has slurred speech on rounds leading to nurses' concern that something is wrong	92

*The top five behaviors as rated by 734 physicians responding to a questionnaire given by Dr. R. G. Niven of the Mayo Clinic to be indicative of impairment problems.

TABLE 2.—*Physician Interventions*

Intervention	*Percent Indicating Agreement (N=734)*
I would be willing to help my colleague's family and to help cover his practice should he need to be admitted to hospital for a problem of psychiatric or chemical dependency	92
I would be uncomfortable but willing to discuss my concern with him	66
I would discuss my concern with other colleagues first	64
I would be willing to participate with a medical society committee in evaluating and advising my colleague even though he or she may be angry and resist the offer of help	61

His sample, while large, is heavily weighted for family practitioners, most of whom probably practice in the Midwest. The Washoe County Medical Society Committee on Major Health Issues, which has responsibility for physician well-being, approved the survey if it was shortened. The board of directors of the society turned the shortened survey down and refused to recommend it to the Nevada State Medical Association. Two major objections were raised in the discussion. The first objection was that if the press got hold of the results it would be damaging to the public image of physicians. This decision was made in a county where four physicians had committed suicide within the previous two years.

In our own work with physicians some interesting patterns have been observed. A Standardized Test of Attitudes and Knowledge (STAK) was developed by the Career Teachers in Alcohol and Drug Abuse.* Validation and reliability studies are being completed. (Copies of the test can be obtained from the author.) The STAK has been given to over 600 clinicians, including 274 physicians attending CME courses on alcohol and drug abuse at various locations across the United States. These physicians volunteered because of their interest in substance abuse and their willingness to complete the attitude survey.

The results concur with Niven's finding that physicians are nonpunitive toward their impaired colleagues. Eighty-five percent disagreed with the statement, "A physician who has been addicted to narcotics should not be allowed to practice medicine again." No age or specialty bias was evident in responses to the above statement. Analysis of variance showed a significant ($P<0.001$) relationship between this nonjudgmental response and high scores on the attitudinal factors of treatment optimism and treatment intervention of the STAK.

The relationship between one's personal experience with chemical dependence and attitudes toward early diagnosis and intervention has not been clear. Table 3 compares the STAK responses of 132 physicians who completed an optional section in which they rated their own dependence on tobacco and alcohol. The data suggest that among physicians who admit to tobacco and alcohol dependence, when compared with physicians who do not, there is greater agreement regarding the importance of early diagnosis and treatment intervention. Both of the items in Table 3 are contained in the treatment intervention factor. This finding may be related to the demonstrated value of peer support in the treatment of alcohol and drug dependence. Many programs for impaired physicians recommend that formerly impaired physicians be included on the confrontation and intervention teams. The attitudinal differences shown in Table 3 may account in part for the greater effectiveness of these physicians in motivating their distressed colleagues to accept help.

Discussion

The above findings suggest that as physicians we are in conflict on the subject of physician impairment. Early in training we begin to develop negative attitudes toward those with alcohol and drug dependency and those with some forms of mental illness. One part of the negative attitude is pessimism about treatment. At the same time, however, we do not wish to punish our impaired colleagues or see them removed from medical practice if they can be treated.

One solution to this dilemma is to consciously

*Tracy L. Veach and Michael Herring assisted with the development of STAK and the analysis of data.

TABLE 3.—*Differences in Attitudes and Chemical Dependence (N=132)**

Attitudinal Statement	*Tobacco-Dependent Physicians (N=36)*	*Alcohol-Dependent Physicians (N=15)*
Physicians who diagnose alcoholism early improve their chance of treatment success.	More Agreement (P 0.05)†	More Agreement (P 0.007)
A person who is dependent on alcohol or drugs cannot be helped until he or she has hit rock bottom.	More Disagreement (P 0.001)	More Disagreement (P 0.05)

*Of 132 physicians who completed the optional section of the STAK, 36 rated themselves as dependent on tobacco and 15 as dependent on alcohol.

†Significance levels determined by x^2 test.

address the problem of attitude change in undergraduate, postgraduate and continuing medical education. Using the principles of participation and experience outlined earlier in this paper, we have been able to show that after a one-week course positive changes occurred in medical students' attitudes toward patients with chemical or alcohol dependency and treatment outcomes.[12] Similar changes in physician attitudes are described by Pursch as a result of a two-week course on alcoholism.[13] On the basis of his experience with 475 physicians he believes that 75 percent of all physicians are unable to deal effectively with alcoholism, either in making an accurate diagnosis or in instituting effective management of the illness. He concludes that "Our trainees have touched many alcoholic livers—but almost no alcoholic lives."

If positive attitudes and behavior toward physician impairment and its treatment are to be developed in all practicing physicians, then intensive educational efforts will be needed. To be effective these programs must have clear goals based on principles that in the past have shown some effectiveness in altering attitudes.

We would suggest a set of educational goals based on those described by Pursch.[13] As a result of educational experiences designed to influence attitudes, medical students and physicians will learn the following:

- Alcohol and drug dependence are treatable illnesses. Treatment of impaired physicians has a high probability of success.[11]
- Effective treatment of impaired physicians needs a structured approach, preferably with a multidisciplinary team.
- Paraprofessionals and formerly impaired physicians are key members of the treatment team.
- Physicians can confront impaired physicians effectively.

These goals can be achieved by involving medical students and physicians in educational experiences characterized by active participation in clinical problems in the classroom and in treatment settings for impaired physicians.

REFERENCES

1. AMA: State disciplinary actions against MD's on rise, Survey Reports. AMA News, Jan 26, 1979

2. Zimbardo P, Ebbesen EB: Influencing Attitudes and Changing Behavior. Reading, MA, Addison-Wesley Publishing Co, 1970

3. Kiesler CA, Collins RE, Miller N: Attitude Change: A Critical Analysis of Theoretical Approaches. New York, John Wiley and Sons, 1969

4. Dressler DM, Prusoff B, Mark H, et al: Clinical attitudes toward the suicide attempter. J Nerv Ment Dis 160:146-155, 1975

5. Reynolds RE, Bice TW: Attitudes of medical interns toward patients and health professionals. J Health Soc Behav 12:307-311, 1971

6. Rezler AG: Attitude changes during medical school: A review of the literature. J Med Educ 49:1023-1030, 1974

7. Fisher JC, Mason RL, Keeley KA, et al: Physicians and alcoholics: The effect of medical training on attitudes toward alcoholics. J Stud Alcohol 36:949-955, 1975

8. Morse RM, Mitchell MM, Martin MA: Physician attitudes toward alcoholism: A positive trend? Currents in Alcoholism 2: 207-224, New York, Grune and Stratton Inc, 1977

9. Frank JD: Persuasion and Healing: A Comparative Study of Psychotherapy, revised edition. Baltimore, Johns Hopkins University Press, 1973

10. Mogar RE, Helm ST, Snedeker MR, et al: Staff attitudes toward the alcoholic patient. Arch Gen Psychiat 21:449-454, 1969

11. Talbott GD, Richardson AC, Atkins EC: The MAG disabled doctor's program: A two year review. J Med Assoc Ga 66: 777-781, 1977

12. Chappel JN, Jordan RD, Treadway BJ, et al: Substance abuse attitude changes in medical students. Am J Psychiatry 134: 379-384, 1977

13. Pursch JA: Physician's attitudinal changes in alcoholism. Alcoholism: Clin Exp Res 2:358-361, 1978

Refer to: Chang A, Kelso G, Harris M, et al: Care of mildly ill children enrolled in day-care centers—Management by parents and by trained home workers (Health Care Delivery). West J Med 134:181-185, Feb 1981

Care of Mildly Ill Children Enrolled in Day-care Centers

Management by Parents and by Trained Home Workers

ALBERT CHANG, MD, MPH; GEORGE KELSO, MD, MPH; MARCIA HARRIS, RN, *and* ALICE JORDAN, BA, *Berkeley, California*

Because child day-care regulations exclude ill children, parents are frequently faced with problems in finding an alternative care arrangement. This pilot study compares home care of mildly ill children by parents (46 preschool children) with care by trained home workers (23 preschool children) during 20 weeks in 1977. Episodes of illness in children cared for by trained home workers showed a slightly shorter duration (median 3.0 days, range 2 to 11 days versus median 5.2 days, range 2 to 14 days) and a less severe course (fewer and milder signs of illness) when compared with episodes of illness in children cared for by parents. Other selected activities involved in the management of the mildly ill children were comparable. Although larger studies are needed, it appears that if parents desire an alternative care arrangement for their children during mild illness, care by a trained home worker may be convenient and safe.

CHILD DAY-CARE REGULATIONS in several states require that centers exclude sick children even when they have minor illnesses.[1] Because several studies have reported that young children enrolled in day-care may have more illnesses than their counterparts cared for at home,[2,3] this policy presents a frequent problem to the children's families. The most available type of care arrangement is, of course, for a parent of the sick child to stay home and care for the child (A. Chang and P. Armstrong, unpublished data, 1977). Although theoretically this might be the choice of most parents, many would like or need acceptable alternative types of care arrangements because they cannot stay at home.

What are some of these alternative care arrangements? One arrangement is care at a sick bay in the day-care center itself. Although Loda and his associates have shown that this is feasible and safe, most day-care centers have neither the space nor the staff to provide this service (oral communication, Berkeley Sick Child Care Project, 1108 F San Pablo, Albany, CA 94706). Another possible care arrangement involves the establish-

From the Department of Social and Administrative Health Sciences, School of Public Health, University of California, Berkeley. Dr. Chang is now affiliated with the UCLA School of Public Health in Los Angeles.

This study was funded by a grant from the Grossman Fund, Committee on Research, School of Public Health, University of California, Berkeley.

Reprint requests to: Albert Chang, MD, MPH, School of Public Health, University of California, Los Angeles, CA 90024.

ment of a separate health center or day-care infirmary that would provide care for the mildly ill children. Such a facility could be set up in a public health agency or in an unused area of a hospital. The authors doubt that such a facility would be readily promoted, however, and we are not aware of the existence of any such centers. A third type of care arrangement is for the child to be cared for at home by an older sibling or other relative, a neighbor, a babysitter or a trained home worker. The Berkeley Sick Child Care Project provides such an arrangement. Using a dial-and-dispatch system it sends, on parental request, a trained home worker to an ill child's own home.[4] These home workers (whose training will be described later) care for the children for part or all of the day during minor illnesses.

In an earlier study of health service needs in day-care centers in Berkeley, California, this type of sick care was designated as the first choice of center directors or health coordinators.[5] Although a preliminary report has described the organization and costs ($3 per hour of care) of such a system, little is known about the actual course and management of the episodes of illness.[6] Our pilot study compares care by parents with care by trained home workers in a sample of preschool children attending a large day-care center in Albany, a small community neighboring Berkeley, which had access to the trained home workers after all the Berkeley requests for care had been met. Comparisons were made of the (1) average duration of illness, (2) presence of certain signs of illness, (3) severity of the signs of illness and (4) medical procedures usually carried out (such as a visit to a physician, temperature recording and administration of medication). Our hypothesis was that the illness episodes of children cared for by the trained home workers would show no differences from those of children cared for by parents in the categories listed above.

Methods

Episodes of mild illness occurring in 69 preschool children enrolled in the Albany Children's Center were monitored during 20 weeks, from January 10, 1977 to May 27, 1977. The monitoring was carried out by an experienced public health nurse who had worked with preschool children in a Head Start project.

Children having episodes of minor illness were recruited into the study sample in the following manner: Each weekday morning the dispatcher at the Berkeley Sick Child Care Project informed the study's public health nurse of any ill child enrolled in the center who would be cared for by a trained home worker in the child's own home. These illness episodes were called the *trained worker care* cases. It should be noted that only those children who were experiencing the first day of illness were recruited into the study. The nurse would then randomly select one or two absent children from the center who were also having their first day of illness but who were being cared for at home by parents. These illness episodes were called the *parent care* cases. In many cases, however, the children actually received both types of care: trained worker care cases were cared for by parents during evenings and nights, on weekends and on holidays; and at times parent care cases were assigned, at some point during the illness, to trained home workers. Thus, the terms parent care cases and trained worker care cases are relative and refer to those illness episodes in which more than half of the days of the illness episode were handled by one of the two types of care arrangement.

A short description of the trained workers is appropriate. The typical home worker was a mature woman who had been a longtime resident of the community and who had some experience in child care either as a parent or as a babysitter. Before working in the Sick Child Care Project, these workers received five weekly two-hour training sessions on first aid, emergency care and care of mildly ill children. The instructors were a nurse and the Berkeley project coordinator, who was an experienced social worker. Following these training sessions, the entire group of eight workers met on a regular monthly basis to discuss common topics of interest and questions that arose during their work with mildly ill children.

The typical routine of the trained worker was as follows: When the worker first arrived at the ill child's home, she obtained some basic information from parents such as signs and symptoms of illness, instruction for care and any special instructions for administration of medications, the work telephone number of the parent or parents and the telephone number of the child's doctor. In addition, the worker completed a daily report describing her activities with the child, medicines administered and any problems that arose. At the end of the illness episode parents were also asked to

complete a worker evaluation report describing their appraisal of the home worker. These reports were usually very positive and favorable.

To monitor the illness episodes, it was necessary to develop a practical illness inventory that would serve as a study instrument. Following the example used by Lakin and her associates,[7] a simple inventory consisting of ten common signs of childhood illness was developed. These were divided into five minor and five major signs, and two degrees of severity, mild and moderate for each sign. The inventory was developed from discussions with both child care workers and parents. The signs labeled as major were those that parents showed the most concern about or that they perceived as being major signs of illness. The minor signs were those that parents felt could be cared for in a group setting, at least in the mild range of seriousness. These opinions and attitudes of parents were obtained in a survey that was conducted concurrently (A. Chang and P. Armstrong, unpublished data, 1977).

The inventory of signs of illness and the two degrees of severity for each sign were arranged as follows: *Minor signs* included (1) cough (coughing occasionally, less often than every ten minutes; coughing frequently, more often than every ten minutes); (2) eye problems (eyes slightly red without exudate; moderately red and/or with exudate); (3) general appearance of fatigue (tired; very tired or listless); (4) reduced activity (half or more of usual activity; less than half of usual activity), and (5) reduced appetite (half or more of usual food intake; less than half of usual intake). The *major signs* included (1) increased temperature (37.7° to 38.8°C [100° to 101.9°F]; 38.9°C [102°F] or above); (2) vomiting (once a day; twice or more a day); (3) diarrhea (one or two loose stools a day; three or more loose stools a day); (4) abnormal breathing (faster than normal—more than 40 breaths per minute, and/or with more effort; breathing noisily, with wheezing or other sounds from the chest), and (5) rhinitis (nose running occasionally, less than every hour, and/or stuffy; running frequently, every hour or more).

During the study, the nurse continued daily monitoring of the episodes of illness until the child became free of any mild major signs of illness and free of any moderate minor signs of illness. This end point was agreed on because it was at that point that the day-care center staff would agree to receive the child back. Each day the nurse would visit the sick child and observe him or her for about ten minutes, recording signs of illness and their severity. Monitoring of illness during weekends and holidays was done by parents using a simple checklist. Parents received written as well as oral instructions for use of this checklist. If a parent forgot to complete the questionnaire, the nurse would call on the following Monday or day after the holiday and ask about the course of illness during the weekend or holidays.

The signs of illness were recorded on an illness episode form, which contained the following information: (1) name of child, (2) illness episode code number, (3) type of care arrangement, (4) age of child, (5) tentative diagnosis, (6) date illness began, (7) date illness ended, (8) duration of illness (in days), (9) ten signs of illness and severity of each sign for each day of illness, (10) visit to doctor, (11) medicine administered, (12) temperature recorded and (13) other medical procedures carried out (such as sponging for fever or forcing of fluids).

During the study each of the two pediatrician-authors made unannounced visits to the sick children to verify the reliability of the nurse's observations. During the 20 weeks 14 paired illness recordings were made which showed a 90 percent agreement between observations made by one of the pediatricians and the study nurse.

Results

In all, 69 preschool children were involved in this study: 46 received parent care (4 were 2 years old, 29 were 3 years old, 11 were 4 years old and 2 were 5 years old) and 23 received trained worker care (5 were 2 years old, 6 were 3 years old, 10 were 4 years old and 2 were 5 years old). There were proportionately more children 3 years of age in the parent care group and fewer that were 4 years of age when compared with the trained worker care children.

A total of 95 separate illness episodes were monitored, 26 trained worker care cases and 69 parent care cases. The small number of cases in each group was due to the fact that on some days no trained home workers were available for the Albany center children because they had been assigned to Berkeley children. In most of the episodes under either type of care, the weekend and holiday monitoring was carried out by the pediatric nurse by telephone.

Table 1 shows that the median durations (in days) of the illness episodes for parent care cases

TABLE 1.—*Duration of Illness, Number of Sign Days, Number of Signs per Episode and Severity of Signs per Episode by Type of Care*

Determination	Parent Care Cases (N=69)	Trained Worker Care Cases (N=26)
	Median Days	Median Days
Duration of illness episodes	5.2*	3.0*
Illness signs per episode†	10.5*	7.0*
Major signs per episode	5.0*	2.5*
Minor signs per episode	6.0*	4.0*
Mild severity signs per episode	8.0*	5.5*
Moderate severity signs per episode	2.5	1.2

*Medians for parent care and trained worker care are significantly different, $P<0.05$ (Mann-Whitney-Wilcox in rank-order test).

†The number of signs in each day were added together to give the number of signs in the whole episode.

and for trained worker care cases were 5.2 and 3.0 days, respectively. The table also gives the median days for the following categories (numbers refer to days for parent care cases and trained worker care cases, respectively): illness signs per episode* 10.5 and 7.0; major signs per episode 5.0 and 2.5; minor signs per episode 6.0 and 4.0; mild signs per episode 8.0 and 5.5, and moderate signs per episode 2.5 and 1.2. There were statistically significant differences in five of the six comparisons above ($P<0.05$ by the Mann-Whitney-Wilcox in rank-order test).

Table 2 shows comparisons of the average number of days that a sign (of either mild or moderate severity) was present, (2) the percent of episodes where a sign (of either mild or moderate severity) was present, and (3) the percent of episodes involving a visit to a physician, administration of medicine, temperature recording and other medical procedures. There were no statistically significant differences in the above four designations.

The first and last days of each illness episode were analyzed for the total number of signs, the numbers of major and minor signs, and the numbers of mild and moderate signs in order to discern any significant differences between the two groups of cases either at the beginning or at the end of the illness episodes. No significant differences were found in any of the above categories between the 26 trained worker care cases and the 69 parent care cases.

Discussion

This pilot study, which compares the home management of mildly ill children enrolled in day-care by parents and by trained home workers, shows that the two types of care arrangements were comparable when certain measurements of illness were monitored. In fact, a number of observations per illness episode such as duration of illness, number of major signs, number of minor signs and number of mild signs indicated that the 26 illness episodes cared for mainly by trained home workers were somewhat milder and of

*The number of signs in each day were added together to give the number of signs in the whole episode.

TABLE 2.—*Comparison of Signs of Illness, Presence of Illness Signs, Management of Illness Episodes and Diagnostic Impressions*

	Parent Care Cases (N=69)	Trained Worker Care Cases (N=26)
Average number of days that sign (of either severity) was present per illness episode		
	Days	Days
Runny nose	4.1	2.9
Cough	2.9	1.9
Reduced activity	1.4	0.8
Reduced appetite	1.2	1.1
Appearance of fatigue	0.9	0.5
Fever	0.7	0.5
Breathing problem	0.2	0.1
Inflamed eyes	0.2	0.1
Diarrhea	0.2	0.1
Vomiting	0.1	0.1
Percent of illness episodes where sign (of either severity) was present		
	Percent	Percent
Runny nose	78.3	73.1
Cough	68.1	57.7
Reduced activity	63.8	61.5
Appearance of fatigue	55.1	50.0
Reduced appetite	52.2	61.5
Fever	40.6	30.8
Vomiting	14.5	7.7
Diarrhea	14.5	7.7
Breathing problem	10.1	7.7
Inflamed eyes	8.7	5.8
Percent of illness episodes with physician visit, administration of medicine, temperature recording and/or other medical procedures done		
	Percent	Percent
Physician visit	29.0	34.6
Administration of medicine	63.8	76.9
Temperature recorded	21.7	23.1
Other medical procedures done	17.4	11.5
Diagnostic impressions		
	Percent	Percent
Upper respiratory infection	66.7	53.8
Diarrhea	11.6	11.5
Fever	7.2	23.1
Otitis media	7.2	7.7
Conjunctivitis	4.3	0.0
Acute laryngitis and tracheitis	1.4	0.0
Eczema and/or dermatitis	1.4	0.0
Chronic pharyngitis and nasopharyngitis	0.0	3.8

slightly shorter duration. Activities involved in the care of both groups of children, such as visits to a physician, administration of medications, temperature recording, and other medical procedures, were comparable between the two types of care arrangements.

What possible explanations could account for the differences in the duration and severity of illness in the episodes noted above? It seems unlikely that the types of illnesses in either group could account for these differences because the presumptive diagnostic impressions were similar in type and percent distribution (Table 2). The characteristics of the first and last days of illness in the episodes monitored were also comparable. Did parents inadvertently prolong the children's stay at home? This also seems unlikely because many of the parents were either students or were employed. Presumably, these parents were interested in shortening the duration of illness as much as possible in order that they themselves could return to school or to work. Were the nurse's observations on the parent care cases unduly severe and critical? There was no evidence of this in the validation visits made by the two pediatricians in the study.

Did the trained home workers provide better care, which in turn resulted in somewhat shorter and milder illnesses? There was no evidence that the care provided by these workers was anything unusual or different from the type of care provided by parents.

Although it was shown above that the characteristics of the first day of illness were comparable in the two groups, an additional explanation could be that parents intuitively wished to provide care for their children whom they thought to be more seriously ill.

It should be emphasized that these slight differences have appeared in a pilot study that compares a relatively small number of illness episodes. Although a future study involving a larger number of illness episodes may show an advantage of one type of care over the other, such a conclusion at this time is not justified.

Nevertheless, as more young children are served in day-care programs, the need for practical alternative care arrangements for them during episodes of mild illness will become more important. Clearly, practicing physicians, especially pediatricians, will become involved with parents and day-care personnel in developing new forms of care arrangement that are safe and feasible.

This pilot study has attempted to show that when families are interested in and desire an alternative care arrangement for their mildly ill children, care by a trained home worker may be a safe and acceptable arrangement.

REFERENCES

1. Minimum Standards for Facilities for Children, California Administrative Code, Title 22, Division 2, Chapter 4

2. Strangert K: Respiratory illness in prechool children with different forms of day care. Pediatrics 57:191-196, Feb 1976

3. Doyle AB: Incidence of illness in early group and family day care. Pediatrics 58:607-613, Oct 1976

4. Loda FA, Glezen WP, Clyde WA Jr: Respiratory disease in group day care. Pediatrics 49:428-437, Mar 1972

5. Chang A, Zukerman S, Wallace HM: Health services needs of children in day care centers. Am J Pub Health 68:373-377, Apr 1978

6. Pedrick NW: Sick Child Care Component in a Day Program: An Evaluation of Process and Outcomes. Menlo Park, California, Stanford Research Institute, Nov 1975 (Mimeo 21 pages)

7. Lakin JA, Anselmo S, Solomons HC: Development of a minor illness inventory for children in day care centers. Am J Pub Health 66:487-488, May 1976

Refer to: Cosby RS, Mayo M, Mirea A, et al: The aging heart—Observations in patients 40 years old and older. West J Med 134:186-189, Feb 1981

Information

The Aging Heart

Observations in Patients 40 Years Old and Older

RICHARD S. COSBY, MD
Pasadena, California
MARY MAYO, BA
ADRIAN MIREA, BS
San Marino, California
JAMES A. PETERSON, PhD
Los Angeles

IN A CONTINUALLY aging geriatric population, precise studies of the heart in senescence have become increasingly important yet, seemingly, have eluded either precise definition or careful study. Interest in the aging process of the heart probably began in the late 19th century with Balfour,[1] but even now, few others than Burch[2] and Pomerance[3] have emphasized its unique problems. The clinical and pathological material presented below is an attempt to analyze the aging process of the heart by identifying those cardiac problems that occur more frequently in older persons and, thus, may be semispecific for this process.

Patients and Methods

Data were available for 3,354 consecutive patients older than 40 years of age, with a primary diagnosis of cardiovascular disease. Patients with minor recurrent cardiac problems (such as recurring arrhythmias or a prolapsed mitral valve) were eliminated from the series.

From the Foundation for Cardiovascular Research, Pasadena, California, and the Emeriti Center, University of Southern California, University Park, Los Angeles.

Dr. Cosby is Clinical Professor of Medicine, Cardiology, Emeritus, USC School of Medicine; and Dr. Peterson is Director of Emeriti Center, USC, University Park, Los Angeles and Professor Emeritus of Sociology, USC; Mr. Mirea is a first year medical student, University of Paris, School of Medicine, and Ms. Mayo is a research assistant.

Reprint requests to: Richard S. Cosby, MD, Foundation for Cardiovascular Research, 201 North El Molino Avenue, Suite 100, Pasadena, CA 91101.

Frequency charts were constructed for all decades over the age of 40 and principal diagnoses were graphed to record incidence by decade for each of the five major types of heart disease.

Pathological data consisted of material obtained from 235 consecutive autopsies. These were reviewed, and an attempt was made to define the principal and subsidiary diagnoses. Data included heart weight, chamber size, evidence of prior myocardial infarction and degree of coronary artery obstruction; the means for each decade were calculated. No specific information was available with regard to precise methods of examination of the coronary arterial tree. In the absence of valvular disease, thickness of the left ventricular wall greater than 15 mm was considered evidence of hypertensive heart disease.

In addition to the above 3,354 consecutive patients, 100 apparently normal patients were selected randomly (20 in each decade) in an attempt to categorize sequential cardiac changes in the later decades of life. In the group of normal subjects, heart rates, mean resting blood pressures, presence of organic murmurs, and electrocardiographic and x-ray film studies were obtained, and decade means compared.

Results

Table 1 lists the principal clinical diagnoses in 3,354 patients older than 40 years of age. The variety of causes of disease was not unexpected, but when separated by decade (see Figure 1), several unusual features were noted. For example, coronary and hypertensive heart disease peaked in the 60- to 70-year age group, but rheumatic disease peaked in the 50- to 60-year age group. Also, heart block appeared as a very significant cause of mortality in the aged.

The relatively high incidence of valvular heart disease in the sixth, seventh and eighth decades deserves further comment. In view of recent information concerning mucinous degenerative valvular disease, and the presence of proven, degenerative aortic disease in the aged, it seems likely that these "valvular" hearts may represent diverse underlying conditions. The increasing incidence of organic murmurs in the aged has been well documented.[4,5]

Table 2 lists the principal causes of death given in the 235 consecutive autopsies. The preponderance of male to female mortality in the 40- to 50-year age group (13 to 1) is striking and is

TABLE 1.—*Clinical Diagnoses in 3,354 Patients 40 Years Old and Older*

Diagnosis	*Number of Cases*
Coronary heart disease	1,774
Hypertensive heart disease	735
Rheumatic heart disease	528
Chronic heart block	145
Acute chronic cor pulmonale	36
Luetic disease	16
Hyperthyroidism	10
Hypothyroidism	26
Cardiomyopathy	18
Tumors	8
Congenital condition	54
Amyloid disease	4

precisely that of prior data.[6] A surprising finding was the relationship of hypertension to total incidence of mortality. The incidence of hypertension (confirmed from thickness of the left ventricular wall) was remarkably high in each decade. In fact, all deaths in patients in the ninth decade showed hypertension and left ventricular hypertrophy.

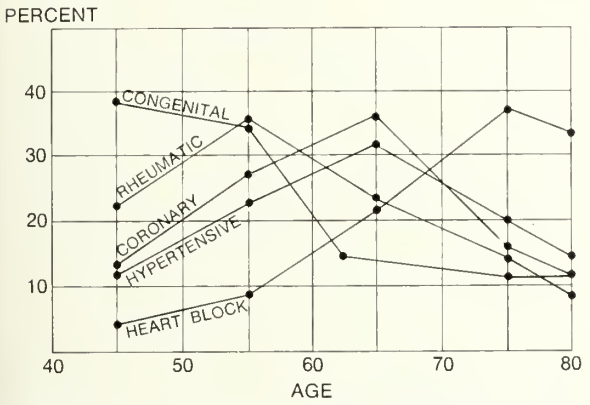


Figure 1.—Incidence of five major types of heart disease by decade in the patients in the study.

A serious disappointment was the lack of autopsy information available on coronary heart disease. The extent of myocardial injury and, particularly, the results of recurrent ischemic changes are two enormously significant clinical events during the life history of coronary artery disease that may escape quantitative evaluation even by a trained pathologist. Although about two thirds of all patients in the fifth and sixth decades were stated to have *clinical* coronary heart disease, as well as hypertension, the relative importance of both hypertension and coronary obstruction was often impossible to evaluate.

Ideally, data on patients in their ninth decade should have provided special information concerning the heart in senescence. Unfortunately, the number of patients was small. The male to female ratio changed substantially and the heart weight decreased strikingly—in this postmortem series it continued to decrease in each decade (Figure 2). Gradual decrease in heart weight after age 70 has been noted previously in both men and women[7] and was clearly related to body weight in this series.

Table 3 lists mean clinical findings by decade of 100 apparently normal patients selected randomly. It is of great interest that the 40- to 50-year age group and the 80- to 90-year age group showed precisely similar male to female ratios as those of the abnormal groups already cited. Heart rate and diastolic pressures apparently did not rise

TABLE 2.—*Principal Clinical Diagnoses in 235 Consecutive Autopsies*

No. of Patients	*Sex*	*Age by Decade*	*HHD*	*RHD*	*CAD*	*LV (mm)*	*INF*	*HWT (grams)*
1	M	10-19	1	1	..	20	..	410
5	2M	20-29	4	1	1	22	1	545
	3F							
8	5M	30-39	6	4	..	14	..	646
	3F							
18	16M	40-49	14	3	11	18	9	505
	2F							
63	45M	50-59	52	14	40	19	23	533
	18F							
69	50M	60-69	56	12	44	18	35	478
	19F							
54	33M	70-79	46	27	38	19	29	471
	21F			3	3			
17	9M	80-89	17	11	9	20	6	422
	8F							

CAD = coronary heart disease; HHD = hypertensive heart disease; HWT = heart weight; INF = positive evidence of previous myocardial infarction; LV = group mean thickness of left ventricular wall; RHD = rheumatic heart disease

with age, but systolic pressures climbed with each decade (Figure 3). Axis and PR intervals appeared to change minimally and sequentially from decade to decade. Although the group numbers are small, the cardiothoracic ratio remained remarkably constant throughout.

Discussion

This study was originally designed to describe a valid geriatric profile. By examining three separate types of data, (1) information on 100 apparently normal persons (40 years old and older and chosen at random from those seeking cardiovascular examination), (2) the spectrum of clinical diagnoses in 3,354 patients older than 40 years and (3) 235 consecutive autopsies of the aged, it was felt that a usable geriatric profile could be delineated. The ideal approach, namely, prospective, would certainly have been hampered by the practical problems of finding a nonmobile geriatric group. Burch[2] has emphasized the enormous complexity produced by the multiple problems of the aged, and the frequency of two or three separate cardiac diagnoses in individual autopsy protocols has already been stressed.

In this study we place greatest emphasis on the frequency and importance of hypertension as a cause of heart disease in the aged. Our measurements of blood pressure levels by decade are similar to those of Harris[3] and many others and appear to represent the increasing afterload re-

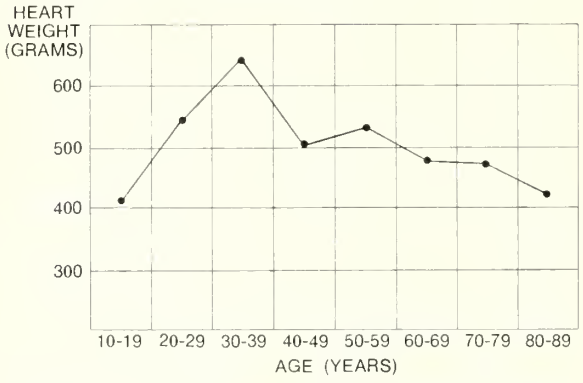


Figure 2.—Measurement of heart weight (grams) by decade in 235 consecutive autopsies, showing a continuous decrease in weight in each decade.

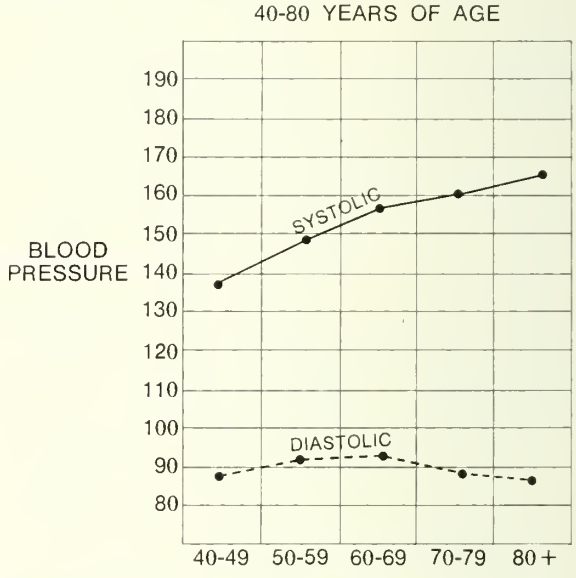


Figure 3.—Blood pressure measurements (mm of mercury) for 100 apparently normal persons selected at random from those seeking cardiovascular examinations (20 in each decade shown).

TABLE 3.—*Clinical Findings by Decade*

Finding	*Decade* 40-49	50-59	60-69	70-79	80+
Mean age	44	53	62	73	82
Sex (male/female)	13/7	9/11	10/10	11/9	8/12
Physical examination					
Heart rate	74	74	78	82	78
Blood pressure	138/88	148/91	156/92	160/89	164/87
Murmurs (percent of sample)	25	15	10	25	15
Electrocardiography					
PR interval (sec)	0.15	0.15	0.17	0.17	0.17
QRS interval (sec)	0.07	0.07	0.06	0.07	0.06
J point elevation (mm)	+0.13	−0.04	+0.02	+0.05	−0.04
ST interval (sec)	0.29	0.30	0.31	0.31	0.31
T wave	2.4	2.3	2.1	2.4	1.7
Axis	7.2	7.0	8.6	8.0	9.5
Radiology					
Cardiothoracic ratio	44% (10)	47% (11)	47% (10)	47% (7)	..

*One hundred normal patients were selected randomly, with 20 subjects in each age group (decade).

lated to stiffness of the aorta and other great vessels. Although the group was small in numbers, all autopsied patients older than 80 years appear to have had hypertensive disease and left ventricular hypertrophy.

In our study by decade of 100 apparently normal subjects, blood pressure, PR interval and axis deviation increased incrementally through each decade. Although the group numbers are small, it was of interest that these findings (with the exception of axis deviation) were reflected in the autopsy data. Gerstenblith and co-workers,[8] using echocardiography, found no increase in thickness of ventricular wall, circumferential fiber shortening, and systolic and diastolic dimensions, in a decade by decade study of a "normal aging population" without evidence of heart disease or hypertension. The single measurement that changed in their series was a decrease in the ejection fraction slope of the mitral valve.

Burch[2] has emphasized the increasing frequency of prolonged PR interval in the aged, finding it "prolonged" in a tenth of 670 patients and noting the concomitant presence of bundle-branch block in a third of these. In this series of patients the highest incidence of heart block occurred in the eighth decade, the highest incidence of both hypertensive and coronary artery disease in the seventh. We consider these three diagnoses then, as typical in reflecting the aging process of the heart. In contrast, and rather surprising, is the "peaking" of the incidence of rheumatic heart disease (certainly, with its onset in youth) in the fifth decade. The greater frequency of heart murmurs with age has previously been noted.[5,6] Additional mucinous and calcific valvular changes may be responsible.

One problem area is coronary artery disease. The elderly rarely give clear descriptions of angina, and the diagnosis of transmural infarction is frequently missed. Our data suggest a decreasing incidence of coronary artery disease in the elderly, but whether this is because of mortality attrition or because of greater difficulties in diagnosis is unclear at present. Perhaps a related finding is the decrease of heart weight with age, which seems illogical in view of the increasing degree of hypertension.

A final problem is the frequency of cardiomyopathy and, in particular, the frequency of infiltrating diseases such as amyloidosis, which has been found in half the autopsies of patients in the tenth decade.[3] The significance of amyloid in producing atrioventricular block and in decreased cardiac compliance has not been established as yet, and it is possible that such deposits may be less significant than generally thought. We agree with Wright and Calkins[9] that amyloidosis, although a relatively common morphologic entity in the aged, is a very rare clinical entity.

Summary and Conclusions

This study has emphasized the rather sharp differences in the frequency of the common forms of heart disease beginning in the fifth decade of life and continuing through each subsequent one.

Two major factors in heart disease in the aged are an increasing prevalence of hypertension and left ventricular hypertrophy (increasing with each decade to 100 percent in the eighth) and a decreasing frequency of coronary artery disease with each decade.

Except for chronic degenerative atrioventricular block (and hypertensive heart disease), no single new entity appeared with frequency among these elderly persons. The prevalence of characteristic lesions in the elderly, such as amyloidosis or aortic valve disease, could not be confirmed in this study.

REFERENCES

1. Balfour GW: The Senile Heart. New York and London, Macmillan & Co., 1894

2. Burch GE: Interesting aspects of geriatric cardiology. Am Heart J 89:99-114, Jan 1975

3. Pomerance A: Cardiac pathology in the aged. Geriatrics 23: 101-114, Apr 1968

4. Bethel CS, Crow EW: Heart sounds in the aged. Am J Cardiol 11:763-767, 1963

5. Harris R: The Management of Geriatric Cardiovascular Disease. Philadelphia, J.P. Lippincott, 1970

6. Cosby R, Giddings J, See J, et al: Late complications of myocardial infarction, *In* Advances of Myocardial Infarction in Spectrum of Ischemia. Basel, S. Karger & Co, 1978, p 73

7. Roessle R, Roulet F: Mass und Zahl in der Pathologie. Berlin and Vienna, J. Springer, 1932

8. Gerstenblith G, Frederikssen J, Yin FCP, et al: Echocardiographic assessment of a normal adult aging population. Circulation 56:273-277, Aug 1977

9. Wright JR, Calkins E: Amyloid in the aged heart: Frequency and clinical significance. J Am Geriatr Soc 23:97-103, Mar 1975

BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

CORRELATIVE NEUROANATOMY & FUNCTIONAL NEUROLOGY—Seventeenth Edition—Joseph G. Chusid, MD, Professor of Neurology, New York Medical College; Director, Department of Neurology, St. Vincent's Hospital and Medical Center, New York City. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1979. 464 pages, $12.00.

This is one of a series of paperback Lange books designed to be a "concise medical library for practitioner and student." This book, as its previous editions, tries to be everything to the neurosciences in 400 pages. It tries to cover the anatomy, physiology and some of the pathology of the brain, the spinal cord, peripheral nerves, autonomic nervous system and muscles. It lists the principles of neurodiagnosis, including not only the neurologic examination but also specialized examinations for aphasia, apraxia, agnosia and the like, and even laboratory evaluations including spinal fluid, electroencephalography, electromyography, other electrodiagnostic techniques, x-ray, cystometry, ophthalmologic tests, audiometry and psychometric tests. It catalogues central nervous system disorders including those in both adults and children as well as psychiatric disorders.

This is clearly a very large task to be accomplished in such a small volume. The results are superficial and the book reads more like a dictionary or a brief encyclopedia than a text. An example of the brevity with which subjects are covered is that the whole area of computerized tomography of the brain is covered in 13 column inches of text plus a few diagrams. Obviously the coverage lacks depth.

In the section on psychiatric disorders archaic concepts like chronic brain syndrome are briefly mentioned, and this syndrome is attributed to chronic alcoholism, cerebral vascular disease, senility, presenility, multiple sclerosis, head trauma, convulsive disorders, brain tumors and neurosyphilis as the most common causes. That list of causes is, in the reviewer's opinion, not inclusive and also is misleading.

In the section on degenerative diseases of the central nervous system brief paragraphs describe senile dementia and presenile dementia, including Pick and Alzheimer diseases. No mention is made of the new and exciting information about transmittable dementias. Evaluation of the entities which are discussed is, again, limited.

In total, the book attempts a task that cannot be accomplished in the number of pages allotted. The result is a catalogue of superficial statements about various aspects of the neurosciences and clinical neurology. It would be of very limited value to either practitioners or students of neurological sciences or clinical neurology. Other better texts are readily available which, while not as concise, provide information in an authoritative and up-to-date fashion and are much more readable.

EARL R. FERINGA, MD
San Diego Veterans Administration Medical Center
San Diego

FUNDAMENTALS OF ABDOMINAL SONOGRAPHY—A Teaching Approach—Howard W. Raymond, MD, Radiologist and Chief of Ultrasound, Department of Radiology, Union-Truesdale Hospital, Fall River, Massachusetts; Clinical Instructor of Diagnostic Radiology, Brown University Medical School, Providence, RI. Grune & Stratton, Inc., Medical and Scientific Publishers, 111 Fifth Ave., New York City (10003), 1979. 200 pages, $23.00. Distributed in the UK by Academic Press, Inc. (London) Ltd., 24/28 Oval Road, London NW1.

This book is a well-written and easy-to-read introduction to clinical applications of static gray-scale ultrasonic imaging. It is divided primarily by region of examination into the following chapters: "Abdominal Sonogram," "Gallstones," "The Dilated Gallbladder," "The Pancreas," "Liver," "Renal Sonography" and "Abdominal Aortic Aneurysms and Other Abdominal Conditions." The initial chapter is a good description of the technique involved in obtaining an adequate examination of the abdomen with a contact B-scanner. It then goes on to illustrate normal anatomy. Each subsequent chapter begins with a brief, practical description of scanning technique differences for that particular area of interest. The bulk of each chapter, and indeed of the book, consists of clinical cases presented in the form of unknowns. The answers are given in the discussions which are pragmatic and often reflect the author's own, apparently extensive, experience as an ultrasonographer. References are sprinkled throughout, without making the book overly academic. A very desirable feature of this book is its repetition of sonograms on the same page as the discussion, obviating the need for flipping pages back and forth. The sonographic images throughout this book are of very high quality. The images are from an instrument with an analogue scan converter and are superior to many generated on the latest state of the art instruments with digital scan converters.

This book would have benefited from a short introductory chapter giving basic physical principles involved in generating an ultrasonic image. This would be particularly helpful for nonradiologists, especially if it were presented in a clear, simplified manner. Certainly, such terms as Mhz, transducer and ultrasonic resolution should have been explained.

Although real-time imaging is mentioned in relation to several cases, its true utility in a modern ultrasonic laboratory is not adequately described or discussed.

Overall, this volume serves as a once-over-lightly introduction to diagnostic ultrasound in the abdomen. For nonradiologists it illustrates some of the broad range of applications of this modality in clinical settings. For radiologists it presents a series of interesting cases with useful discussions.

KAI HABER, MD
Associate Professor of Radiology
University of Arizona Health Sciences Center
Tucson, Arizona

in memoriam

California Medical Association

AMSEL, MAXWELL R., Redondo Beach. Died November 13, 1980, aged 85. Graduate of Columbia University College of Physicians and Surgeons, New York, 1920. Licensed in California in 1943. Dr. Amsel was a member of the Los Angeles County Medical Association.

BOSTWICK, JACK R., JR., Glendora. Died September 11, 1980, aged 65. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1941. Licensed in California in 1941. Dr. Bostwick was a member of the Los Angeles County Medical Association.

BRONSTEIN, IVAN, Belvedere-Tiburon. Died November 19, 1980 in Belvedere, aged 45. Graduate of the University of Ottawa Faculty of Medicine, 1960. Licensed in California in 1962. Dr. Bronstein was a member of the San Francisco Medical Society.

CARSWELL, JOHN H., Santa Barbara. Died December 8, 1980, aged 84. Graduate of the Medical College of Georgia, Augusta, 1953. Licensed in California in 1958. Dr. Carswell was a member of the Medical Society of Santa Barbara County.

CHAPMAN, PAUL J., Alhambra. Died September 13, 1980, aged 62. Graduate of Creighton University School of Medicine, Omaha, 1949. Licensed in California in 1950. Dr. Chapman was a member of the Los Angeles County Medical Association.

CHILDREY, JOHN H., San Jose. Died November 6, 1980 in Carmel, aged 77. Graduate of the Medical College of Virginia, Richmond, 1926. Licensed in California in 1931. Dr. Childrey was a retired member of the Santa Clara County Medical Society.

CRATON, JEAN, Palo Alto. Died December 7, 1980 of cancer, aged 54. Graduate of Indiana University School of Medicine, Bloomington-Indianapolis, 1953. Licensed in California in 1954. Dr. Craton was a member of the Santa Clara County Medical Society.

EINHORN, BENJAMIN, Tarzana. Died August 12, 1980, aged 80. Graduate of the University of Illinois College of Medicine, Chicago, 1937. Licensed in California in 1937. Dr. Einhorn was a member of the Los Angeles County Medical Association.

FARRELL, ELLISTON, Laguna Hills. Died October 26, 1980, aged 76. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1930. Licensed in California in 1946. Dr. Farrell was a member of the Los Angeles County Medical Association.

FOOTER, WILSON, Oakland. Died December 12, 1980 in Oakland of heart disease, aged 68. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1940. Licensed in California in 1940. Dr. Footer was a member of the Alameda-Contra Costa Medical Association.

FOX, ERNEST T., Palm Springs. Died November 16, 1980 in Newport Beach, aged 78. Graduate of the University of Southern California School of Medicine, Los Angeles, 1943. Licensed in California in 1943. Dr. Fox was a retired member of the Riverside County Medical Association.

GELFAND, BEN, Long Beach. Died June 26, 1980, aged 70. Graduate of the Chicago Medical School, 1943. Licensed in California in 1957. Dr. Gelfand was a member of the Los Angeles County Medical Association.

GOODWIN, MARVIN H., Los Angeles. Died July 19, 1979, aged 60. Graduate of the University of California Medical School, Berkeley-San Francisco, 1944. Licensed in California in 1944. Dr. Goodwin was a member of the Los Angeles County Medical Association.

LANGE, HARRY W., Bakersfield. Died December 18, 1980 in Bakersfield of leukemia, aged 83. Graduate of Northwestern University Medical School, Chicago, 1928. Licensed in California in 1933. Dr. Lange was a retired member of the Kern County Medical Society.

MANNING, THOMAS P., Pasadena. Died January 18, 1980, aged 90. Graduate of the University of Alabama School of Medicine, Birmingham, 1911. Licensed in California in 1916. Dr. Manning was a member of the Los Angeles County Medical Association.

MARK, ARTHUR E., Los Angeles. Died April 20, 1980, aged 90. Graduate of the University of Minnesota Medical School, Minneapolis, 1915. Licensed in California in 1923. Dr. Mark was a retired member of the Los Angeles County Medical Association.

MCCANDLISS, ROBERT J., Seal Beach. Died December 5, 1980 in Seal Beach, aged 84. Graduate of the University of Michigan Medical School, Ann Arbor, 1921. Licensed in California in 1953. Dr. McCandliss was a retired member of the Orange County Medical Association.

MCEWEN, WILLIAM L., Bakersfield. Died in June 1980, aged 76. Graduate of Rush Medical College, Chicago, 1936. Licensed in California in 1936. Dr. McEwen was a retired member of the Kern County Medical Society.

PATTERSON, J. KENNETH, Santa Barbara. Died November 19, 1980 in Santa Barbara, aged 76. Graduate of Harvard Medical School, Boston, 1929. Licensed in California in 1935. Dr. Patterson was a retired member of the Medical Society of Santa Barbara County.

PINTO, PETER SAMUEL, Ridgecrest. Died December 16, 1980 in Ridgecrest of heart disease, aged 52. Graduate of the University of Illinois College of Medicine, Chicago, 1952. Licensed in California in 1953. Dr. Pinto was a member of the Kern County Medical Society.

PRATT, ORLYN B., Los Angeles. Died September 25, 1980 of injuries sustained in automobile accident, aged 81. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1924. Licensed in California in 1924. Dr. Pratt was a member of the Los Angeles County Medical Association.

PUTTLER, OLIVER L., Alhambra. Died June 14, 1980, aged 70. Graduate of Temple University School of Medicine, Philadelphia, 1936. Licensed in California in 1942. Dr. Puttler was a member of the Los Angeles County Medical Association.

ROBERTSON, ELLIOTT, Long Beach. Died August 16, 1980, aged 54. Graduate of Meharry Medical College, Nashville, 1953. Licensed in California in 1956. Dr. Robertson was a member of the Los Angeles County Medical Association.

ROBUCK, JAMES C., Visalia. Died December 9, 1980 in Visalia of injuries sustained from fall, aged 62. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1952. Licensed in California in 1953. MD degree from California College of Medicine, 1962. Dr. Robuck was a member of the Tulare County Medical Society.

SLOAN, JULIUS, Culver City. Died November 6, 1980, aged 82. Graduate of the University of Minnesota Medical School, Minneapolis, 1933. Licensed in California in 1944. Dr. Sloan was a member of the Los Angeles County Medical Association.

STEPHENS, MARGARET A., San Francisco. Died December 18, 1980, aged 40. Graduate of the Women's Medical College of Pennsylvania, Philadelphia, 1966. Licensed in California in 1969. Dr. Stephens was a member of the San Francisco Medical Society.

STILLMAN, FREEMAN L., Seal Beach. Died September 7, 1980, aged 77. Graduate of the University of Nebraska College of Medicine, Omaha, 1932. Licensed in California in 1940. Dr. Stillman was a member of the Los Angeles County Medical Association.

VINETZ, JOSEPH C., Los Angeles. Died November 11, 1980 in Los Angeles, aged 79. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1927. Licensed in California in 1927. Dr. Vinetz was a member of the Los Angeles County Medical Association.

WONG, MICHAEL W., Walnut Creek. Died December 9, 1980, aged 45. Graduate of Temple University School of Medicine, Philadelphia, 1960. Licensed in California in 1963. Dr. Wong was a member of the Alameda-Contra Costa Medical Association.

YUSKIS, ANTON S., El Cajon. Died November 18, 1980, aged 72. Graduate of Rush Medical College, Chicago, 1936. Licensed in California in 1936. Dr. Yuskis was a member of the San Diego County Medical Society.

Utah State Medical Association

DE MARS, HAROLD VICTOR, Ogden. Died November 3, 1980 in Ogden, aged 65. Graduate of the University of Oregon Medical School, Portland, 1941. Licensed in Utah in 1948. Dr. De Mars was a member of the Weber County Medical Society.

FARR, KEITH FREDERICK, Ogden. Died December 16, 1980 in Ogden, aged 60. Graduate of George Washington University School of Medicine, Washington, DC, 1944. Licensed in Utah in 1946. Dr. Farr was a member of the Weber County Medical Society.

What they didn't teach you in medical school.

They should have taught Billing along with Biology nd Biochemistry.

Because that's the area where many professional ractices are hurting. Maybe your practice has classic ymptoms—delays, delinquencies, cash flow problems.

But not to worry. Bank of America has an antidote.)ur Professional Practice Management Service (PPM).

PPM is a computerized billing system that com- iles, processes, stuffs and mails your statements in a action of the time it now takes manually.

We offer three flexible input methods designed to ieet the needs of your particular practice: personal- ed; hand-written Account Entry Forms; computer rminals that let you key input directly from your ffice; or our innovative Audio Response feature where ou talk to the computer using your push-button lephone as a terminal.

PPM also automatically prepares insurance forms. /hich means we can relieve you of extra processing burdens brought on by new Medi-Cal requirements.

And PPM can give you daily reports listing the status of your accounts, while providing automatic bookkeeping and posting services.

Quite simply, PPM can save you time and money. We know because we've been serving the California health care industry for over 15 years. Currently, more than 1000 professionals use our Professional Practice Management Service.

And it costs less than what you might expect. After all, we're specialists in our field, as you are in yours.

So if you're suffering from acute billing problems, call us in the morning for more information.

It could be all it takes to make your practice perfect.

BANK OF AMERICA

Corporate Electronic Banking

For more information about Bank of America's Professional Practice Management, call: Mike Wisber (415) 622-4651 or Dan DeMarco (213) 683-3742. Or mail this coupon to Bank of America, Corporate Electronic Banking, P.O. Box 37000, San Francisco, California 94137.

Name_____

Medical Offices _____

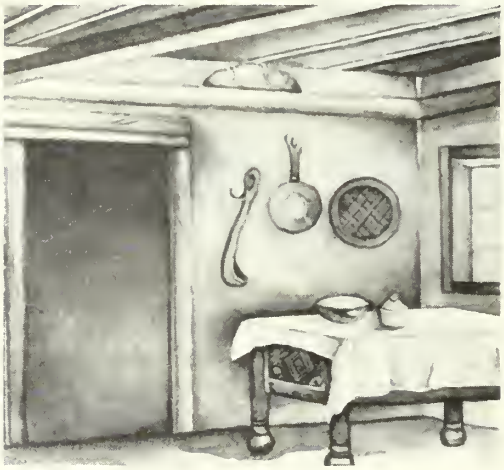
Street_____

City/State/Zip_____

Bank of America NT&SA • Member FDIC

Yesterday's Folk Remedy:

A rye loaf in the rafters.



Early in this century in Central Europe, almost every farm family kept a loaf of moldy rye bread on one of the kitchen beams. When any family member was cut or bruised, it was an old custom to cut a thin slice from the outside of the loaf, mix it into a paste with water, and apply it to the wound with a bandage. It was believed that no infection would then result from the cut.[1]

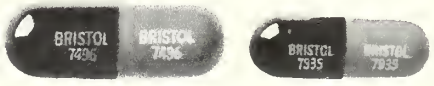
Today's Tradition: Tegopen® (cloxacillin sodium)

for the treatment* of known or suspected staphylococcal infections such as:

- Acute sinusitis
- Furunculosis and carbuncles
- Impetigo
- Secondarily infected dermatitis
- Cellulitis
- Abscesses
- Infected sebaceous cysts

In serious, deep-seated staph infections, 500 mg q.i.d. dosage is recommended.†

- Tegopen has been reported active against 96% of *Staphylococcus aureus*.[2]
- 80% of *S aureus* has been reported resistant to amoxicillin and ampicillin.‡[2]
- 88% of *S aureus* has been reported resistant to penicillins G and V.‡[2]
- Staph resistance to erythromycin may develop during a course of therapy.[3]



Available as 500-mg and 250-mg capsules and Oral Solution 125 mg/5 ml.

Tegopen® (cloxacillin sodium) Today's Penicillin for Today's Physician

1. Florey HW, Chain E, Heatley NG, et al: *Antibiotics*. London, Oxford University Press, 1949, p 2
2. Bac-Data Bacteriologic Report, Professional Market Research, 1978-1979. The clinical significance of *in vitro* data is unknown
3. Erythromycin prescribing information (in *Physicians' Desk Reference*, ed 34. Oradell, NJ, Medical Economics Co, 1980) states that staph resistance may develop during treatment

See brief summary of prescribing information on an adjoining page.

Copyright © 1981, Bristol Laboratories

*Note: The choice of Tegopen should take into consideration the fact that it has been shown to be effective only in the treatment of infections caused by pneumococci, Group A beta-hemolytic streptococci, and penicillin G-resistant and penicillin G-sensitive staphylococci. If the bacteriology report later indicates that the infection is due to an organism other than a penicillin G-resistant staphylococcus sensitive to cloxacillin sodium, the physician is advised to continue therapy with a drug other than cloxacillin sodium or any other penicillinase-resistant semisynthetic penicillin.

†In serious, life-threatening infections, oral preparations of the penicillinase-resistant penicillins should not be relied on for initial therapy.

‡Not all isolates may have been tested using both discs.

Tegopen®
(cloxacillin sodium)
Capsules and Oral Solution

Brief Summary of Prescribing Information

For complete information, consult Official Package Circular
(12) 9/11/75

INDICATIONS:

Although the principal indication for cloxacillin sodium is in the treatment of infections due to penicillinase-producing staphylococci, it may be used to initiate therapy in such patients in whom a staphylococcal infection is suspected. (See Important Note below.)

Bacteriologic studies to determine the causative organisms and their sensitivity to cloxacillin sodium should be performed.

IMPORTANT NOTE

When it is judged necessary that treatment be initiated before definitive culture and sensitivity results are known, the choice of cloxacillin sodium should take into consideration the fact that it has been shown to be effective only in the treatment of infections caused by pneumococci, Group A beta-hemolytic streptococci, and penicillin G-resistant and penicillin G-sensitive staphylococci. If the bacteriology report later indicates the infection is due to an organism other than a penicillin G-resistant staphylococcus sensitive to cloxacillin sodium, the physician is advised to continue therapy with a drug other than cloxacillin sodium or any other penicillinase-resistant semi-synthetic penicillin.

Recent studies have reported that the percentage of staphylococcal isolates resistant to penicillin G outside the hospital is increasing, approximating the high percentage of resistant staphylococcal isolates found in the hospital. For this reason, it is recommended that a penicillinase-resistant penicillin be used as initial therapy for any suspected staphylococcal infection until culture and sensitivity results are known.

Cloxacillin sodium is a compound that acts through a mechanism similar to that of methicillin against penicillin G-resistant staphylococci. Strains of staphylococci resistant to methicillin have existed in nature and it is known that the number of these strains reported has been increasing. Such strains of staphylococci have been capable of producing serious disease, in some instances resulting in fatality. Because of this, there is concern that widespread use of the penicillinase-resistant penicillins may result in the appearance of an increasing number of staphylococcal strains which are resistant to these penicillins.

Methicillin-resistant strains are almost always resistant to all other penicillinase-resistant penicillins (cross-resistance with cephalosporin derivatives also occurs frequently). Resistance to any penicillinase-resistant penicillin should be interpreted as evidence of clinical resistance to all, in spite of the fact that minor variations in *in vitro* sensitivity may be encountered when more than one penicillinase-resistant penicillin is tested against the same strain of staphylococcus.

CONTRAINDICATIONS:

A history of a previous hypersensitivity reaction to any of the penicillins is a contraindication.

WARNING:

Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents, e.g., pressor amines, antihistamines, and corticosteroids.

Safety for use in pregnancy has not been established.

PRECAUTIONS:

The possibility of the occurrence of superinfections with mycotic organisms or other pathogens should be kept in mind when using this compound, as with other antibiotics. If superinfection occurs during therapy, appropriate measures should be taken.

As with any potent drug, periodic assessment of organ system function, including renal, hepatic, and hematopoietic, should be made during long-term therapy.

ADVERSE REACTIONS:

Gastrointestinal disturbances, such as nausea, epigastric discomfort, flatulence, and loose stools, have been noted by some patients. Mildly elevated SGOT levels (less than 100 units) have been reported in a few patients for whom pretherapeutic determinations were not made. Skin rashes and allergic symptoms, including wheezing and sneezing, have occasionally been encountered. Eosinophilia, with or without overt allergic manifestations, has been noted in some patients during therapy.

USUAL DOSAGE:

Adults: 250 mg. q 6h.

Children: 50 mg./Kg./day in equally divided doses q 6h. Children weighing more than 20 Kg. should be given the adult dose. Administer on empty stomach for maximum absorption.

N.B. INFECTIONS CAUSED BY GROUP A BETA-HEMOLYTIC STREPTOCOCCI SHOULD BE TREATED FOR AT LEAST 10 DAYS TO HELP PREVENT THE OCCURRENCE OF ACUTE RHEUMATIC FEVER OR ACUTE GLOMERULONEPHRITIS.

SUPPLIED:

Capsules—250 mg. in bottles of 100; 500 mg. in bottles of 100.
Oral Solution—125 mg./5 ml. in 100 ml. and 200 ml. bottles.

BRISTOL®
Bristol Laboratories
Division of Bristol-Myers Company
Syracuse, New York 13201

MEDICAL DIRECTOR (JAPAN)

SmithKline Corporation, a world leader in the health care field, has a challenging new opportunity in Tokyo for a medically-trained professional to serve as Medical Director for our Japanese joint venture operation. The incumbent will provide medical expertise/guidance on new and established products, coordinate medical dialogue between the parent companies and participate in strategy/policy regarding clinical investigation, medical claims and product safety.

The ideal candidate will be fluent in both Japanese and English, have a desire to live in Japan and possess training/experience in internal medicine. This well-rounded professional should also possess a broad business prospective and be sensitive to the marketing consequences of the drug development process, including product claims and safety. Some traveling will be required to handle these responsibilities, as well as attend scientific symposia. Opportunity for clinical activity is available and encouraged.

We offer a competitive salary/benefit package, including an attractive relocation policy. Interested candidates should submit their curriculum vitae including professional areas of interest and salary requirements to:
Donald C. Schaller,
Area Personnel Manager - Japan,
SMITHKLINE CORPORATION
1504 Spring Garden Street,
P.O. Box 7929, Philadelphia PA. 19101
or phone (215) 854-7843.
Equal Opportunity
Employer,
M/F/H/V.

SmithKline CORPORATION

(Continued from Page 16)

PHYSICIANS WANTED

GENERAL/FAMILY PRACTICE PHYSICIANS (2) needed by 31 member multi-specialty group. Excellent practice opportunity; benefits and retirement program; all practice costs paid; early shareholder status. Reply D. R. Molesworth, Administrator, San Luis Medical Clinic, Ltd., 1235 Osos Street, San Luis Obispo, CA 93401.

ASSOCIATES WANTED

FAMILY PHYSICIAN or other primary care: To associate with long-established board certified FP. Recent ultra-modern medical office in high income area of Orange County. Major hospital close by. Community college and Calif. State Univ. in area, teaching—UCI. Write Box 6155, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

FULL-TIME ASSOCIATE to join non-surgical orthopedic practice. Examinations, conservative care and reports required for on-the-job injured patients. Please send curriculum vitae to the Medical Director, Franklin Medical Group, 7060 Hollywood Blvd., Suite 240, Los Angeles, CA 90028, or call (213) 467-4298.

INTERNIST to join general internist, currently in solo practice in Salt Lake City. Prefer general internist: certain subspecialties also suitable. Write Box 6173, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

FOR SALE

1978 Continental Compere head x-ray unit, registered and utilized for low-volume work. Also, Norelco dental processor.
Price negotiable. Call or write.

William S. Halsey, MD
1087 Devonshire Dr., #312
Encinitas, CA 92024
(714) 436-7077

SITUATIONS WANTED

FAMILY PRACTITIONER board qualified. Licensed California, Oregon, Washington, Minnesota. Age 47. Interested in all opportunities, prefer group practice, ER work, industrial medicine, metropolitan or rural practice. Full or part time. Contact Robert L. Stein, MD, 1215 First Ave., No. Sauk Rapids, MI 56379. Tel (612) 255-0467.

INFECTIOUS DISEASE-INTERNIST. University trained, 30, ABIM certified. ID Board eligible. Desires opportunity in Infectious Disease/Internal Medicine in or near San Diego. Available July 1981. N. Kollisch, MD, 33 Pond Ave., Brookline, MA 02146. Tel (617) 566-0875.

GASTROENTEROLOGIST, 37, ABIM, American Grad. trained in all phases of endoscopy, additionally in laparoscopy, PTC, ERCP and esophageal motility. Prefer California and Southwestern U.S. Presently on faculty, available immediately. Box 6166, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

CARDIOLOGIST, mature FMG, BC Int. Med. & CV. Looking for a small hospital or a group who are looking for a cardiologist, ideally but not exclusively, to start invasive arterial pressure monitoring, pacemakers & echocardiography. Box 6176, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

LEGAL COUNSEL
SAMUEL SPITAL, ESQ.
1200 Third Avenue, Suite 1200
San Diego, CA 92101, (714) 231-4848
Former DEPUTY ATTORNEY GENERAL representing the Board of Medical Quality Assurance and Dept. of Health. Now specializing in B.M.Q.A. and defense malpractice matters throughout California.

SITUATIONS WANTED

INTERNIST—30, ABIM certified, moving to San Diego July 1981. Seeks position in Internal Medicine. Reply Box 6167, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

RADIOLOGISTS: Plan your 1981 vacation early. Board Certified coverage for your practice. Licensed all western states. Reserve early for best selection of dates. For further information reply c/o Box 6159, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

GASTROENTEROLOGIST, 35, broad experience in clinical gastroenterology and all-APP major procedures. Desire Southern California area, available July 1981. Jack D. Goldin, MD, 1274 Ocean Parkway, Brooklyn, NY 11230.

WOMAN PHYSICIAN in early sixties, in good health, seeks part-time position, 1-2 days/week, in psychiatry and/or general medicine in Catholic hospital, institution or office within 50 mi. radius of San Francisco or Truckee in California. Practice must be under physician willing to supervise, as probationary requirement of BMQA. Write to: Physician, Box 6165, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

CARDIAC REHABILITATION: Internist with ACSM Program Director Certification and 2 year University Fellowship in Clinical Exercise Physiology and Cardiac Rehabilitation, and 1 year experience in designing and working as Medical Director of a private Cardiac Rehabilitation Clinic seeks a position as Medical Director of Exercise Physiology and Cardiac Rehabilitation Facility, preferably with university affiliation. Box 6164, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

RADIOLOGIST, 50, CERTIFIED. Previous fellowships in cardiovascular and neuroradiology. Expertise various forms special procedures. 5 years experience neuro CT. Presently director of neuroradiology and special procedure section of large busy university affiliated hospital with faculty appointment. No preference as to location. Write Box 6157, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

HEMATOLOGIST-ONCOLOGIST needed for busy, aggressive practice of same in Northern California community, one and a half hours from San Francisco. Teaching available. Send CV to Box 6153, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PATHOLOGIST, 45, certified AP-CP, excellent references, seeks relocation to San Francisco-San Jose area for permanent full-time or part-time practice. Box 6110, The Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PULMONARY INTERNIST, University trained, ABIM, trained all phases of pulmonary medicine; seeks practice opportunity; available July 1981. Box 6141, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

RADIOLOGIST, excellent credentials, desires part-time film reading. Will do routine work or expert Neuro CT consultation. Can travel. Box 6174 Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

INTERNIST, board-eligible, 30, family practice experience, seeks associateship or small group practice in Northern California or Southern Oregon. Available Mid-July, 1981. Ted W. Grace, MD, 2700 S. Holly St. Unit 205, Denver, CO 80222.

RADIOTHERAPIST—Boards, long experience private hospital. Prefer half-time. Northern California. Will consider any California location. Reply Box 6169, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PEDIATRICIAN, 30, passed written Boards, Flex, seeks to relocate in California (Solo, Hospital based, Clinic). 1½ years in private practice. Reply Box 6175, The Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PSL
PRACTICE SALES & LOCATIONS
BUY • SELL • LEASE
EVALUATIONS • FINANCE
17942 Skypark Circle, Ste D, Irvine, CA 92714
(714) 641-9203
General/Family—Internal Medicine
Industrial/Multi-Specialty Clinics and other specialties
LOCATIONS
For Lease—Medical Bldgs—For Sale
APPRAISALS
Comprehensive practice and property appraisals
ASSOCIATESHIPS
Placement services—Partnerships
Financing, Practice/Property Management

SITUATIONS WANTED

INTERNIST—certified, ICU fellowship complete, 33, interest and training in cardiology. Excellent references, available now, prefer California coast. Box 6178, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

OB/GYN, 36, Univ. trained, graduated Perinatalogy Fellowship. Cal. licensed. Seeking solo, group partnership or assume practice in Southern Cal. Box 6179, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

INTERNIST, 33, Board Certified, University trained, seeks position in Napa Valley or nearby area. Write Box 6180, The Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

CARDIOLOGIST WITH M.P.H., 37, University trained in invasive and noninvasive cardiology. Desires association with group of cardiologists, internists, or hospital based private practice in Pacific Northwest or Northern California. Box 6181, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

MEDICAL PRACTICES AVAILABLE

BUYING or SELLING any type Medical Practice contact California Professional Practices, 2555 Huntington Dr., Suite D, San Marino, CA 91008. (213) 796-9262 or Agent Mr. Reilly (805) 543-4782 or Cliff Rauch (714) 997-0853.

PROFESSIONAL PRACTICE OPPORTUNITIES—Dermatology, Internal, Ophth, EENT, ENT, Otolaryngology, Family, Pediatrics, others available. To buy or sell any type practice, partnership, or for placement contact Mary Bradshaw, 21 Altamount, Orinda, CA 94563. (415) 376-0762.

MEDICAL SPACE AVAILABLE in Lincoln, CA, near Sacramento. Developer is seeking G.P.-Family Physician, OB/GYN, Fediatrician, Internal Medicine, Urologist to locate within new 21,000 sq. ft. Medical Ctr. to be completed February 1981. Facilities include Lab, X-ray and Pharmacy. Excellent growth area. Hewlett Packard and Shugart and Assoc. Electronics Cos. building in vicinity with 5,000 to 15,000 new employees. Will finish to suit. Contract R.S. Mgmt. Co., 541 Jefferson Ave. Suite 107, Redwood City, CA 94063. Call (415) 365-6400.

INSTANT OFFICE AVAILABLE—Open practice tomorrow in new fully furnished MD's office located a block from the hospital in beautiful fast growing Auburn, CA. Reasonable rent. (916) 671-2200.

(Continued on Page 38)

(Continued from Page 37)

LOCUM TENENS WORK WANTED

RADIOLOGIST, 50, board certified with board experience in general radiology and diagnostic ultrasound. Available for locum tenens work. Prefer Northern California. Jack Scott, MD, 11898 Forest View Dr., Nevada City, CA 95959. (916) 272-9304.

LOCUM TENENS WANTED

LOCUM TENENS: Prestigious Sports Medicine/ Preventive Medicine Center needs a board certified internist experienced in Stress Testing and giving complete physicals for one month, anytime early 1981. Write Box 6182, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

WYOMING: Emergency Medicine—Summer locum tenens for experienced emergency physicians in busy resort hospital located in Jackson, Wyoming. Average of 56 hours per week with flexible scheduling arrangement. Must be available June 5 through September 14 inclusive, without exception. Excellent hourly compensation plus paid professional liability insurance. For further information, contact William Salmo at 1-(800)-525-3681 (in Colorado call collect (303) 471-4981).

OFFICE FOR SALE

PHYSICIANS OFFICE FOR SALE in large established medical complex. Medical Center Co., Provo, Utah. 6 percent of entire complex's assets. Approximately 4,000 sq. ft. (includes full basement). Set up for two physicians with common lab. Negotiable terms or will rent. Contact: Ken Kartchner, 717 No. 450 East, Orem, UT 84057.

FHP is Growing...

Grow with us!

We have opportunities for Physicians to join our multi-specialty group HMO in Salt Lake City

For more information, contact Ralph Brown Telephone (801) 355-1234

FHP FAMILY HEALTH PROGRAM

323 South 600 East, Salt Lake City, Utah 84102

THE HOSPITAL of the GOOD SAMARITAN

presents

OVARIAN CANCER

WEDNESDAY
FEBRUARY 25, 1981

Los Angeles HILTON

Distinguished Faculty:

HUGH R. K. BARBER, MD ..... *New York, NY*
OTIS A. GADDIS, MD ..... *Los Angeles, CA*
C. PAUL MORROW, MD ..... *Los Angeles, CA*
RICHARD H. NALICK, MD ..... *Los Angeles, CA*
JOHN B. SCHLAERTH, MD ..... *Los Angeles, CA*
JAMES TATE THIGPEN, MD ..... *Jackson, MS*
J. DONALD WOODRUFF, MD ..... *Baltimore, MD*
Course Director: RICHARD H. NALICK, MD

FEES:
$70 MD's, $30 Interns, Residents, Fellows, Retired MD's, other Allied Health Professionals

This course is acceptable for 7 hours Category I Credit towards the CMA and AMA certificates in Continuing Medical Education.

Registration for Ovarian Cancer Symposium
February 25, 1981

Name _____

Specialty _____ Phone _____

Address _____

City _____ Zip _____

Make check payable to: OVARIAN CANCER

Mail check and registration form to:
"OVARIAN CANCER SYMPOSIUM"
Hospital of the Good Samaritan
616 So. Witmer Street
Los Angeles, CA 90017

For more information, contact:
MARY JANE THOMPSON
Coordinator of Symposia
(213) 488-8908

(Continued from Page 27)

April 6-8—**Third Annual Orange County Ob/Gyn Congress.** Orange County Obstetrical and Gynecologic Society and UCI at Newporter Inn, Newport Beach. Monday-Wednesday. 24 hrs. $250. Contact: Orange Co. Ob/Gyn Soc., P.O. Box 1297, Orange 92668. (714) 978-1260.

April 10-11—**26th Annual T. Hart Baker, MD, Obstetrics and Gynecology Symposium.** Southern Calif. Permanente Medical Group at South Coast Plaza Hotel, Costa Mesa. Friday-Saturday. Contact: Lilia M. Guerrero, SCPMG, Dept. of Ed. and Research, 4747 Sunset Blvd., 4th Fl., Los Angeles 90027. (213) 667-4241.

April 25-30—**American College of Obstetricians and Gynecologists.** Convention Center, Las Vegas. Saturday-Thursday. Contact: W. H. McDannel, Convention Mgr., ACOG, 1 E. Wacker Dr., Suite 2700, Chicago 60601. (312) 222-1600.

May 11-13—**Recent Advances in Obstetrics and Gynecology.** UCSD at Vacation Village, San Diego. Monday-Wednesday. 18 hrs.

June 10—**Carcinomas of the Uterus and Ovaries.** See Cancer, June 10.

PEDIATRICS

February 17-20—**Epilepsy in Childhood and Adolescence—32nd Annual Western Institute on Epilepsy.** See Medicine, February 17-20.

March 5-7—**Advances in Pediatrics.** Children's Hospital Medical Center of Northern Calif. at Sahara Hotel, South Lake Tahoe. Thursday-Saturday. Contact: Gretchen Hayes, Med. Staff Office, CHMC, 51st and Grove Sts., Oakland 94609. (415) 428-3334.

March 12-15—**Clinical Pediatrics.** American Academy of Pediatrics, Calif. Chap. 2, at Hilton Riviera, Palm Springs. Thursday-Sunday. $160, members; $185, nonmembers. Contact: Calif. Chap. 2, AAP, P.O. Box 2134, Inglewood 90305. (213) 757-1198.

April 3-4—**Pediatric Topics.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday.

April 8-10—**Update in Pediatric Pulmonary and Intensive Care.** See Medicine, April 8-10.

May 2-3—**The Physician and the Handicapped Child: New Directions.** American Academy of Pediatrics and State Dept. of Education at Sacramento. Saturday-Sunday. Contact: Peter Miller, MD, Marin Co. Civic Ctr., Rm. 280, Dept. of Health and Human Services, San Rafael 94903. (415) 499-6877.

May 4-8—**11th Annual Review of Pediatrics.** USC. Monday-Friday. $300.

May 6-8—**Care of the Sick Newborn—6th Annual Symposium.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. Contact: Prog. Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

May 13—**Genetic Counseling.** LLU. Wednesday. 4 hrs. $30.

May 13—**Pediatric Symposium.** American Heart Assn.-Greater Los Angeles Affiliate and Los Angeles Pediatric Soc. at USC. Wednesday. 6 hrs. Contact: LaVerna M. Titus. AHA-GLAA, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

May 14-16—**Advances in Pediatrics.** UCSF at Mark Hopkins Hotel, San Francisco. Thursday-Saturday.

May 20-25—**Pediatrics for the Primary Care Physician and All That Jazz.** UCD at Sacramento. Wednesday-Monday.

PSYCHIATRY

March 2-4—**Biobehavioral Science for Psychiatrists.** STAN. Monday-Wednesday. 15 hrs. $225.

March 4-8—**7th International Gender Dysphoria Symposium.** Univ. of Nevada School of Medicine and Harry Benjamin International Gender Dysphoria Assn. at Cal-Neva Lodge, Lake Tahoe. Wednesday-Sunday. $150. Contact: Marjorie Cutler, Cont. Med. Ed., College Inn, Univ. of Nevada, Reno 89557. (702) 784-4046.

March 6-7—**Common Sexual Dysfunctions: Diagnosis and Treatment.** UCLA. Friday-Saturday. 10 hrs.

April 2-4—**Short-Term Dynamic Psychotherapy.** UCSD at Hilton, San Diego. Thursday-Saturday. 17 hrs. $300.

April 3-5—**Cults, Religiosity and the Adolescent.** UCSF. Friday-Sunday.

April 12-14—**Family Problems, Aging and Sexuality.** See Of Interest To All, April 12-14.

June 28-30—**Family Problems, Aging and Sexuality.** See Of Interest To All, June 28-30.

July 8-10—**Update in Psychiatry: Psychopharmacology.** UCSD at Hanalei Hotel, San Diego. Wednesday-Friday.

July 31-August 1—**Innovations: New Trends in Family Therapy, Brief Therapy and Family Medicine.** Mental Research Institute at Sheraton-Palace, San Francisco. Friday-Saturday. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

RADIOLOGY AND PATHOLOGY

February 18-20—**Anaerobic Bacteriology Methods.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. 15 hrs. Contact: Program Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

February 25-27—**Minicomputers, Microcomputers and Big Computers.** American Society of Clinical Pathologists at Monterey. Wednesday-Friday. 19½ hrs. Contact: Admin. Asst., Education Center, 2100 W. Harrison St., Chicago 60612. (312) 738-1336.

February 27-March 1—**Neuroradiology.** USC. Friday-Sunday. 20 hrs. $200.

February 28—**Cytology Workshop.** UCLA. Saturday.

March 4-7—**Sierra Radiology Conference—2nd Annual.** Sacramento Radiology Research and Education Foundation and Northern Calif. Radiological Society at North Lake Tahoe. Wednesday-Saturday. 18 hrs. $245. Contact: Michael H. Reid, PhD, MD, Sacramento Radiology Research and Education Fndn., P.O. Box 161112, Sacramento 95816.

March 6-8—**Current Approaches to Radiation Oncology, Biology and Physics.** UCSF at Fairmont Hotel, San Francisco. Friday-Sunday.

March 8-13—**19th National Conference on Breast Cancer.** See Cancer, March 8-13.

March 9-13—**Diagnostic Radiology.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday. $350.

March 13-19—**College of American Pathologists/American Society of Clinical Pathologists—Joint Spring Meeting.** Town and Country, San Diego. Friday-Thursday. Contact: Joan Lipe, CAP, 7400 N. Skokie Blvd., Skokie, IL 60077. (312) 677-3500.

March 14-15—**B-Scan Ultrasonography: Update.** UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday.

April 11-18—**Hawaii Imaging Conference.** American College of Medical Imaging at Kauai Surf Hotel, Kauai, Hawaii. One week. 23½ hrs. Contact: ACMI, P.O. Box 27188, Los Angeles 90027. (213) 275-1393.

April 25—**Cytodiagnosis in Medical Practice.** UCLA. Saturday. 6 hrs. $125.

May 2-9—**Liver Pathology Workshop.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

May 24-29—**The Pathologist as a Clinical Consultant.** UCD at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

June 3-5—**Radiology in the Emergency Room.** UCSF at Golden Gateway Holiday Inn, San Francisco. Wednesday-Friday.

June 16-19—**Society of Nuclear Medicine.** Hilton, Las Vegas.

Tuesday-Friday. 28 hrs. $60, members; $120, nonmembers. Contact: Registrar, SNM, 475 Park Ave. S., New York 10016. (212) 889-0717.

August 16-21—**23rd Annual Postgraduate Course in Dermal Pathology.** Memorial Hospital Medical Center-UCI Center for Health Education at Newporter Inn, Newport Beach. Sunday-Friday. Contact: Program Coordinator, Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

Postgraduate Videotape Programs in Diagnostic Radiology. Developed by Dept. of Radiology, UCSF. 27 programs in all aspects of diagnostic radiology. Outstanding national and international guest lecturers in addition to UC staff present basic approaches to radiographic interpretation and technique as well as new research and clinical advances. Contact: Radiology Postgraduate Ed. Section, UCSF, Dept. of Rad., Rm. M396, San Francisco 94143. (415) 666-5731, between 7:00 a.m. and 4:00 p.m.

SURGERY

Februry 20-22—**Pathophysiology and Techniques of Cardiopulmonary Bypass.** See Medicine, February 20-22.

February 23-25—**American Society for Surgery of the Hand—36th Annual Meeting.** Las Vegas. Monday-Wednesday. Contact: ASSH, 2600 S. Parker Rd., Suite 132, Aurora, CO 80014. (303) 755-4588.

February 26-March 3—**American Academy of Orthopaedic Surgeons.** Convention Center, Las Vegas. Thursday-Tuesday. Contact: AAOS, 444 N. Michigan Ave., Chicago 60611.

March 1-6—**Symposium on Facial Surgery.** Sacramento Society of Otolaryngology and Maxillo-Facial Surgery at South Lake Tahoe. Sunday-Friday. 26 hrs. $35. Contact: Sacramento Soc. of Otolaryngology and Maxillo-Facial Surgery, P.O. Box 3213, El Macero 95618.

March 1-13—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. 13 days. Contact: Mrs. Mona Bolton, ERI, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

March 5-7—**Calculi.** American Urological Association at Sheraton Harbor Island Hotel, San Diego. Thursday-Saturday. Contact: AUA, Office of Education, Texas Med. Ctr., 4th Fl-Inst. of Religion Bldg., 1129 Wilkins, Houston, TX 77030.

March 6-7—**Ophthalmology Update.** UCD, PMC, UCSF, STAN at Sheraton Palace, San Francisco. Friday-Saturday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062.

March 11—**Common Fractures and Joint Injuries.** LLU. Wednesday. 4 hrs. $30.

March 21-22—**ECG Course for Oral and Maxillofacial Surgeons.** UCSF. Saturday-Sunday.

March 22-April 3—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. 13 days. Contact: Mrs. Mona Bolton, ERI, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

March 25-28—**4th Annual U.S. IOL Symposium.** American Intra-Ocular Implant Society at Century Plaza Hotel, Los Angeles. Wednesday-Saturday. Contact: Debbi Miller, Dir. of Mtg. Services, Am. Intra-Ocular Implant Soc., P.O. Box 3140, Santa Monica 90403. (213) 829-7317.

March 26-28—**Retina Workshop.** St. Mary's Hospital and Medical Center at Ahwahnee Lodge, Yosemite. Thursday-Saturday. 12 hrs. $225. Contact: Retina Research Fund, St. Mary's Hosp. and Med. Ctr., 450 Stanyan St., San Francisco 94117.

March 26-29—**Pediatric Surgery of the Head and Neck: A Frontier Symposium.** The Institute for Medical Education and Research and UCSD at Silverado Country Club and Resort, Napa Valley. Thursday-Sunday. 20 hrs. Contact: The Institute for Medical Education and Research, 135 Dickinson St., San Diego 92103.

March 28-29—**Common Problems in Urologic Medicine: Initial Evaluation and Management.** UCSF. Sunday-Monday.

April 4-8—**Seminar on Controversial Surgery—18th Annual.** UCLA at Hilton Riviera, Palm Springs. Saturday-Wednesday. 18 hrs. $295.

April 5-10—**Management of Maxillofacial Trauma.** Sacramento Society of Otolaryngology and Maxillo-Facial Surgery at South Lake Tahoe. Sunday-Friday. 32 hrs. $400. Contact: Sacramento Soc. of Otolaryngology and Maxillo-Facial Surgery, P.O. Box 3213, El Macero 95618.

April 8—**Urology.** St. Francis Medical Center, Lynwood. Wednesday. 6 hrs. Contact: Allan M. Hoffman, EdD, Dir. of Med. Ed., St. Francis Med. Ctr., 3630 Imperial Highway, Lynwood 90262. (213) 603-6174.

April 8-11—**Facial Plastic Surgery: Aesthetic Contouring of the Face and Neck.** UCSF at Stanford Court, San Francisco. Wednesday-Saturday. 21 hrs. $350.

April 8-12—**Symposium on Vascular Surgery—9th Annual.** UCLA at Hilton Riviera, Palm Springs. Wednesday-Sunday. 17 hrs. $315.

April 9-10—**Diseases of the Urinary Tract.** STAN at Rickey's Hyatt House, Palo Alto. Thursday-Friday. 16 hrs. $200.

April 9-11—**General Surgery.** UCSF. Thursday-Saturday.

April 23-24—**XII Jules Stein Lecture and Annual Postgraduate Seminar—Anterior Segment Disease: Current Update on Immunology, Corneal Disease, Refractive Surgery, and Contact Lenses.** Jules Stein Eye Institute, Los Angeles. Thursday-Friday. 16 hrs. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024. (213) 825-4617.

April 25—**Radial Keratotomy Workshop.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024. (213) 825-4617.

May 9-16—**Management of the Surgical Patient.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 25 hrs. $295.

May 21-22—**Neurosurgery—11th Annual Postgraduate Course.** UCSF. Thursday-Friday.

May 21-23—**Retina Workshop.** St. Mary's Hospital and Medical Center at Quail Lodge, Carmel Valley. Thursday-Saturday. 12 hrs. Contact: Retina Research Fund, St. Mary's Hosp. and Med. Ctr., 450 Stanyan St., San Francisco 94117.

May 22-23—**Vitrectomy-Ocutome Workshop.** PMC. Friday-Saturday. 12 hrs. $450.

June 1-5—**Intensive Course in Refractive Keratoplasty: Barraquer Technique.** Jules Stein Eye Institute, Los Angeles. Monday-Friday. $1,500. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024.

June 5-6—**Ophthalmology Update.** UCD, PMC, UCSF, STAN at Sheraton-Palace, San Francisco. Friday-Saturday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062.

June 6-12—**Orthopaedic Review Course.** UCSF at Golden Gateway Holiday Inn, San Francisco. One week.

June 20-27—**Ophthalmology.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. $350.

June 26-27—**Surgery Trauma.** UCLA. Friday-Saturday.

OF INTEREST TO ALL PHYSICIANS

February 19-22—**Winter Sports Injuries.** UCD at Ahwahnee Hotel, Yosemite. Thursday-Sunday. 14 hrs.

February 20-21—**Pain: New Approaches to Treatment.** Mesa Vista Hospital and Vista Hill Foundation at Hotel del Coronado, Coronado. Friday-Saturday. Contact: Virginia Everett, Vista Hill Fndn., 7798 Starling Dr., San Diego 92123. (714) 278-6761.

February 23-27—**Basic Science for Clinicians.** STAN. Monday-Friday. 25 hrs. $295.

February 26-27—**Therapeutic Drug Monitoring.** PMC. Thursday-Friday. 12 hrs. $85.

March 1-5—**Medical Evaluation of the Preoperative Patient.** UCD at Ahwahnee Hotel, Yosemite. Sunday-Thursday.

March 3-June 30—**Family Medicine.** USC. Tuesdays; 7:00-10:15 p.m. 56 hrs. $325.

March 5-6—**Sports Medicine Symposium—Women in Sports.** Sonoma County Medical Assn., Community Hospital of Sonoma Co., Sonoma State Univ., and Foundation for Medical Care of Sonoma Co. at Sonoma State Univ., Rohnert Park. Thursday-Friday. 7½ hrs. $50. Contact: William Tewksbury, Sonoma Co. Med. Assn., 3033 Cleveland Ave., Santa Rosa 95401. (707) 544-2014.

March 5-8—**Critical Care Medicine.** USC at Las Vegas. Thursday-Sunday.

March 5-8—**Sports Medicine.** UCD at Hyatt Lake Tahoe, Incline Village. Thursday-Sunday.

March 6-7—**Advances in Alcoholism—2nd Annual Symposium.** Raleigh Hills Foundation and American Medical Society on Alcoholism at Registry Hotel, Newport Beach. Friday-Saturday. 17 hrs. $150. Contact: Raleigh Hills Fndn., 17861 Cartwright Rd., Irvine 92714. (800) 854-3020 or (714) 641-1616.

March 7-8—**Approaches to Healing.** San Diego County Medical Society and UCSD at San Diego. Saturday-Sunday. 12 hrs. Contact: SDCMS, Medicine and Religion Committee, P.O. Box 23015, San Diego 92123.

March 7-8, 21-22—**Annual Hypnosis Workshop.** San Francisco Academy of Hypnosis at Children's Hospital, San Francisco. Two weekends. 28 hrs. $260. Contact: Jan Brooks, SFAH, 2820 15th Ave., San Francisco 94114.

March 12-15—**4th Annual Symposium on Patient Education.** UCSF at Golden Gateway Holiday Inn, San Francisco. Thursday-Sunday. $150.

March 13-15—**Clinical Management.** STAN at The Lodge, Pebble Beach. Friday-Sunday. 8 hrs.

March 13-18—**California Medical Association—110th Annual Session.** Disneyland Hotel, Anaheim. Friday-Wednesday. Contact: Joan Kammerer, CMA.

March 14—**Current Concepts in Antibiotic Therapy**. Fresno Community Hospital. Saturday. Contact: Joann Ellis, Education and Training Dept., Fresno Community Hosp., P.O. Box 1232, Fresno 93715. (209) 442-6000, ext. 5696.

March 16-20—**Sports Medicine.** University of Hawaii at Princess Kaiulani Hotel, Waikiki, Honolulu. Monday-Friday. 18 hrs. $230. Contact: Joy Lewis, Box CE-CCECS, 2530 Dole St., Honolulu 96822. (808) 948-8244.

March 16-27—**Intensive Residency in Occupational Medicine, Session II.** UCSF. Two weeks.

March 18-20—**Recent Advances in Clinical Nutrition.** UCSD at Vacation Village, San Diego. Wednesday-Friday. 17 hrs.

March 21—**Alcoholism and Its Treatment: 1981.** UCD at Hotel El Rancho Racquet Resort, Sacramento. Saturday. 7½ hrs.

March 21-22—**Sleep and Biological Rhythms.** UCSD. Saturday-Sunday.

March 25-29—**Human Dimensions in Medicine.** UCSD at Vacation Village, San Diego. Wednesday-Sunday. 26 hrs. $400.

April 1-2—**Symposium on Infectious Diseases.** Sutter Community Hospitals at Northeast Holiday Inn, Sacramento. Wednesday-Thursday. 14 hrs. $85. Contact: Sutter General Hospital, Cont. Med. Ed., 2820 L St., Sacramento 95816. (916) 454-2222, ext. 1430.

April 8—**Psychiatry for the Non-Psychiatrist.** LLU. Wednesday. 4 hrs. $30.

April 8—**Rehabilitation of the Elderly Patient.** La Palma Intercommunity Hospital and UCI at South Coast Plaza Hotel, Costa Mesa. Wednesday. $75. Contact: Ingrid Humphrey, La Palma Intercommunity Hosp., 7901 Walker St., La Palma 90623. (714) 522-0150.

April 11-12—**Nutrition for the Primary Care Physician.** UCSF. Saturday-Sunday. 14 hrs. $125.

April 11-18—**Office Management of Chronic Pain.** Univ. of Washington School of Medicine at Wailea Beach, Maui. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

April 11-18—**Drug Therapy.** Univ. of Washington School of Medicine at Royal Lahaina, Maui. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

April 12-14—**Family Problems, Aging and Sexuality.** USC. Sunday-Tuesday. 18 hrs. $136.

April 23-25—**Postgraduate Institute.** CMA at Ahwahnee Hotel, Yosemite. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

April 23-26—**Wound Management Workshop.** UCSD at Hilton, San Diego. Thursday-Sunday. 20 hrs.

April 24-25—**Fluid and Electrolytes.** PMC. Friday-Saturday. 12 hrs.

April 25-26—**Pharmacokinetics '81.** Memorial Hospital Medical Center—UCI Center for Health Education, Long Beach. Saturday-Sunday. Contact: Prog. Coordinator, Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

April 25-May 2—**Diagnostic and Therapeutic Skills.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $350.

May 1-2—**Annual Spring Seminar.** Providence Hospital at Claremont Hotel, Oakland. Friday-Saturday. Contact: Providence Hosp., Med. Staff Office, Box 23020, Oakland 94623. (415) 874-8003.

May 5-11—**Basic Diving Medicine.** UCSF. One week.

May 11-15—**Postgraduate Institute for Primary Care Physicians —Symposium on Non-Emergency Outpatient Care.** UCSD at Vacation Village, San Diego. Monday-Friday. 27 hrs. $275.

May 16-17—**Eating Disorders.** UCLA. Saturday-Sunday.

May 17-22—**Fingers-to-the-Toes: An Orthopedic Approach for the Family Physician.** UCD at Stanford Sierra Lodge, Fallen Leaf Lake. Sunday-Thursday.

May 31-June 6—**Family Practice Refresher Course.** UCLA at Miramar-Sheraton, Santa Monica. One week.

June 7-13—**Family Practice Refresher Course.** UCI at Disneyland Hotel, Anaheim. One week. 53 hrs. Contact: Cont. Ed. in Health Sciences, UCI Extension, P.O. Box AZ, Irvine 92716. (714) 833-5414.

June 8-12—**Family Practice Board Review Course.** UCSF. Monday-Friday.

June 10-12—**6th Annual Conference on Hyperbaric Oxygen.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. Contact: Program Coordinator, Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

June 12-14—**Clinical Update.** American Medical Association at Hilton, San Francisco. Friday-Sunday. Contact: AMA Dept. of Meeting Services, 535 N. Dearborn St., Chicago 60610. (312) 751-6000.

June 18-20—**Human Sexuality.** CMA at Claremont Resort, Oakland. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

June 28-30—**Family Problems, Aging and Sexuality.** USC. Sunday-Tuesday. 17¼ hrs. $136.

August 16-21—**9th Annual Family Practice Refresher Course.** UCD at Hyatt Del Monte, Monterey. Sunday-Friday. 36 hrs.

Needs Identification and Fulfillment Tailored to the Individual (NIFTI). UCSF. A new contemporary approach to formal continuing medical education. Participating physicians identify their own CME needs which will be met by a program specifically tailored by UCSF faculty for each individual physician. 25 hrs. minimum; 100, maximum. Fee: $350; $200, UCSF alumni. Contact: Extended Programs in Medical Education, 569-U, Univ. of Calif., San Francisco 94143. (415) 666-4251.

Audio-Digest Foundation—A nonprofit subsidiary of CMA. Provides by subscription twice-a-month tape recorded summaries of leading national meetings and authoritative surveys of current literature. A catalog of lectures and panel discussions in all areas of medical practice is also available. Contact: Audio-Digest Foundation, 1577 E. Chevy Chase Dr., Glendale 91206.

Videotape Postgraduate Course for the Primary Care Physician. UCSF, School of Medicine, Div. of Ambulatory and Community Medicine. 24 Category I hrs. upon completion of course as designed—12 programs each year. Contact: Ms. Estelle Nelson, UCSF, Rm. 432-A, 400 Parnassus Ave., San Francisco 94143. (415) 666-1445.

ALASKA, MONTANA and IDAHO

This list of continuing education programs in Alaska, Montana and Idaho is supplied by the University of Washington School of Medicine's program of regional medical education in Washington, Alaska, Montana and Idaho (WAMI). To have events listed, please send information to: WAMI Program, CME Calendar, D-207 Health Sciences Building, School of Medicine, SC-64, University of Washington, Seattle, Washington 98195; or phone (206) 543-6995.

ALASKA

March 19—**Right Brain Functioning—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday, 7:30 pm-9:30 pm. Alaska Psychiatric Institute Medical Library. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99503. (907) 274-7579.

March 25—**Gardnerella Vaginalis Vaginitis—Univ. of Wash. Ob/Gyn Sessions** (Anchorage). Wednesday, 12-1 p.m. Providence Hospital. Contact: Hedric Hanson, MD, 3300 Providence Drive, Anchorage, AK 99504. (907) 276-8385.

April 30—**Group Therapy—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday, 7:30 pm-9:30 pm. Alaska Psychiatric Institute Medical Library. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99503. (907) 274-7579.

May 27—**Univ. of Wash. Ob/Gyn Session** (Anchorage). Wednesday, 12-1 p.m. Providence Hospital. Contact: Hedric Hanson, MD, 3300 Providence Drive, Anchorage, AK 99504. (907) 276-8385.

June 18—**Consultation on Adolescent Problems/Systems Approach—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday, 7:30 pm-9:30 pm. Alaska Psychiatric Institute Medical Library. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99503. (907) 274-7579.

MONTANA

February 18-20—**Adolescent Medicine—Univ. of Wash. Internal Medicine Review Sessions.**

February 18, Wednesday, Great Falls. 5-7:30 p.m. Deaconess Hospital. Contact F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

February 19, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: D. Frank Johnson, MD, Marillac Hall, Billings, MT 59101. (406) 657-7083.

February 20, Friday, Missoula. 8-10:30 a.m. St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

March 5-7—**Montana Section, American College of OB/Gyn Annual Meeting.** Big Sky. Thursday-Saturday. Contact: John T. Browne, MD, 2825 Fort Missoula Rd., Missoula, MT 59801.

March 6-7—**Topics in Internal Medicine.** Big Sky. Friday-Saturday. Contact: D. Frank Johnson, MD, Marillac Hall, Billings, MT 59101. 406) 657-7083.

March 25-27—**New Developments in Cardiology—Univ. of Wash. Internal Medicine Review Sessions.**

March 25, Wednesday, Great Falls. 5-7:30 p.m., Columbus Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

March 26, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: D. Frank Johnson, MD, Marillac Hall, Billings, MT 59101. (406) 657-7083.

March 27, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

April 15—**Pediatric Psychiatry—Univ. of Wash. Pediatrics Sessions** (Great Falls). Wednesday. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

April 22-24—**Congenital Heart Disease in Adults—Univ. of Wash. Internal Medicine Review Sessions.**

April 22, Wednesday, Great Falls. 5-7:30 p.m., Deaconess Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

April 23, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: D. Frank Johnson, MD, Marillac Hall, Billings, MT 59101. (406) 657-7083.

April 24, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

May 27-29—**Office Endocrinology—Univ. of Wash. Internal Medicine Review Sessions.**

May 27, Wednesday, Great Falls. 5-7:30 p.m. Columbus Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

May 28, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: D. Frank Johnson, MD, Marillac Hall, Billings, MT 59101. (406) 657-7083.

May 29, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

June 10—**Allergy—Univ. of Wash. Pediatrics Sessions** (Great Falls). Wednesday. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

IDAHO

February 21-28—**Sports Medicine.** Sun Valley. Saturday-Saturday. Elkhorn Inn. Contact: Univ. of Wash. School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 16—**Gyn Oncology—Univ. of Wash. Ob/Gyn Sessions** (Boise). Monday. 12-1 p.m., St. Luke's Hospital. Contact: David M. Barton, MD, 999 N. Curtis Rd., Boise, ID 83706. (208) 385-9391.

March 17—**Infectious Diseases—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12-1 p.m., St. Anthony Hospital. Contact: David Fischel, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

May 18—**Evaluation and Treatment of Premature Labor—Univ. of Wash. Ob/Gyn Sessions** (Boise). Monday. 12-1 p.m., St. Luke's Hospital. Contact: David M. Barton, MD, 999 N. Curtis Rd., Boise, ID 83706. (208) 385-9391.

May 19—**Psychiatry—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12-1 p.m., St. Anthony Hospital. Contact: David Fischel, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

OREGON

This bulletin of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue. Roseburg 97470:

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

University of Oregon Medical School, Department of Psychiatry, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, University of Oregon Medical School. Contact: Dept. of Psychiatry, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8144.

University of Oregon Medical School, Department of Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, University of Oregon Medical School. Contact: Dept. of Medicine, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8607.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, OR 97213. (503) 234-8211.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00-9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee, P.O. Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Third Annual

UC-RIVERSIDE-NICHOLS INSTITUTE SYMPOSIUM

on

Cellular and Molecular Endocrinology

Friday, April 3-Saturday, April 4, 1981

On the University of California-Riverside campus at the foot of the Box Springs Mountains

The purpose of the meeting is to foster communication among scientists who are interested in the cellular, biochemical and structural aspects of endocrinology. The meeting will have four approximately three hour sessions devoted to the topics of (a) Neuro-Active Peptides, (b) Structure Functions, (c) Hormone Localization, (d) Calcium-Secretion Coupling.

Fourteen internationally recognized scientists will present lectures on their work in these areas. They include the following: R. A. Bradshaw (St. Louis), C. V. Byus (Riverside), W. L. Duax (Buffalo), M. G. Farquhar (New Haven), W. H. Fletcher (Riverside), E. Herbert (Eugene), S. M. McCann (Dallas), A. R. Means (Houston), F. Naftolin (New Haven), J. G. Pierce (Los Angeles), H. Rasmussen (New Haven), B. H. Satir (Bronx), W. Stumpf (Chapel Hill), and J. Walsh (Los Angeles).

Registration fees for the meeting are $25.00 per participant ($15.00 for postdoctoral student/fellow; $10.00 for student) and $125.00 for physicians wishing to enroll in the Continuing Medical Education (CME) Program (Category I) through the UC-Los Angeles School of Medicine.

For registration and further information please write:

ENDOCRINOLOGY SYMPOSIUM
DEPARTMENT OF BIOCHEMISTRY
UNIVERSITY OF CALIFORNIA
RIVERSIDE, CA 92521
PHONE: (714) 787-5093

$25,000,000 LOAN FUND

Available to Physicians

Up to $20,000 Entirely by Mail!

Emphatically private. All transactions through plain, unmarked mail. Use the money for anything. We don't ask.

Attractive rates. Turn-around a few short days.

Call **Ron Malcomb** or send coupon for short-form package. It's brief and easy!

THE BANKERS INVESTMENT COMPANY

(213) 577-3049

99 SOUTH LAKE, SUITE 260
LOCK DRAWER JM-1 • P.O. BOX 4602
PASADENA, CALIFORNIA 91101

MR. R. J. MALCOMB, BANKERS INVESTMENT CO
LOCK DRAWER JM-1, P.O. BOX 4602
PASADENA, CALIFORNIA 91101

AMOUNT I WANT $ _____

NAME _____

ADDRESS _____

CITY _____ STATE _____

ZIP _____ PHONE _____

EMERGENCY MEDICINE

June 4-6—**Update: Emergency Medicine.** Sponsored by the Oregon Chapter of ACEP, EDNA and OSEMTA. Thursday-Saturday. Salishan Lodge, Gleneden Beach, Oregon. For additional information please contact: Regina Atcheson, MD, c/o E/PCP Program, Good Samaritan Hospital & Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center, Portland. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-7590.

February 9-13—**Twelfth Annual Family Practice Review.** Portland. Monday-Friday. Marriott Hotel. Contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8700.

OBSTETRICS AND GYNECOLOGY

October 1-3—**Pacific Northwest Review of Obstetrics & Gynecology.** Thursday-Saturday. Thunderbird-Jantzen Beach, Portland, Oregon. For additional information please contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, Portland, OR 97201. (503) 226-1555.

SURGERY

March 6-7—**Difficult and Reoperative Abdominal Surgery.** Friday-Saturday. Downtown Red Lion, Portland, Oregon. For additional information please contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, Portland, OR 97201. (503) 226-1555.

INTEREST TO ALL PHYSICIANS

April 2-3—**Current Concepts in Drug Therapy.** Portland. Thursday-Friday. Jantzen Beach Thunderbird. For additional information please contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, Portland, OR 97201. (503) 225-8700.

April 8-10—**School of Medicine Alumni Association Scientific Sessions and Sommer Memorial Lectures.** University of Oregon Health Sciences Center Campus. For additional information please contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, Portland, OR 97201. (503) 225-8700.

September 11-12—**Ashland Conference: Gastroenterology.** Friday-Saturday. Ashland Hills Inn, Ashland, Oregon. For additional information please contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, Portland, OR 97201. (503) 226-1555.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. Please send information to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle 98121; or phone (206) 623-4801.

February 14-21—**Sports Medicine. Sun Valley,** ID. Saturday-Saturday. U/W at Elkhorn Inn, Sun Valley, ID. Contact: U/W School of Medicine.

February 21-28—**Perinatal Critical Care.** Sun Valley, ID. Saturday-Saturday. U/W at Elkhorn Inn, Sun Valley, ID. Contact: U/W School of Medicine.

February 21-28—**Practical Neurology.** Ilikai, Honolulu, Hawaii. Saturday-Saturday. U/W at Ilikai, Honolulu, Hawaii. Contact: U/W School of Medicine.

February 21-28—**Metabolism and Endocrinology.** Kona, Hawaii. Saturday-Saturday. U/W at Kona Surf, Kona, Hawaii. Contact: U/W School of Medicine.

February 23—**Emergency Medical Services—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD. P.O. Box 489. Wenatchee, WA 98801. (509) 663-8711.

February 26-27—**Burns: Care & Prevention.** Thursday-Friday. St. Joseph Hospital. Tacoma. Contact: CME Pierce County.

February 27—**Diagnosis and Treatment of Common Arthritic Diseases.** Seattle. Friday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

March 6-7—**Clinical Pharmacology for the Practitioner.** Seattle. Friday-Saturday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

March 6-7—**Trauma.** Friday-Saturday. Tacoma General Hospital. Contact: CME Pierce County.

March 7—**Handicapped Child.** Seattle. Saturday. Contact: U/W School of Medicine.

March 12-13—**Tacoma Academy of Internal Medicine.** Tacoma. Thursday-Friday. Contact: CME Pierce County.

March 16—**Gyn Oncology—Univ. of Wash. OB/GYN Sessions** (Spokane). Tuesday. 12-1 p.m., Sacred Heart Medical Center. Contact: Wm. Harvey Frazier, MD, West 101 8th Ave., Spokane, WA 99204. (509) 838-8347.

March 17—**Epilepsy.** Spokane. Tuesday. Contact: U/W School of Medicine.

March 19-21—**Pediatric Rehabilitation.** Thursday-Saturday. Mary Bridge Childrens' Hospital. Tacoma. Contact: CME Pierce County.

March 23—**Pain—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

March 23-27—**Advances in Family Practice.** Seattle. Monday-Friday. Contact: U/W School of Medicine.

March 27—**Sexually Transmitted Diseases.** Seattle. Friday. Contact: U/W School of Medicine.

March 30—**Diabetes.** Seattle. Monday. Northwest Hospital. Contact: Marilyn Carlson, Northwest Hospital Education

COURSE SPONSORS AND CONTACT INFORMATION

CME PIERCE COUNTY—Contact: Mrs. Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON) — Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Sandra McDonald, Division of Continuing Medical Education, Virginia Mason Medical Center, 1100 Ninth Avenue, Seattle, WA 98101. (206) 223-6898.

and Training Department, 1551 N 120th, Seattle, WA 98133. (206) 364-0500 ex. 1737.

March 30-April 10—**Rehabilitation Medicine Review.** Seattle. Monday-Friday. Contact: U/W School of Medicine.

April 3—**Nutrition in the Hospitalized Patient.** Seattle. Friday. Contact: U/W School of Medicine.

April 4—**Mason Clinic Day.** Seattle. Saturday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

April 4-11—**Current Concepts in OB/GYN.** Kona, Hawaii. Saturday-Saturday. U/W at Kona Surf, Kona, Hawaii. Contact: U/W School of Medicine.

April 11-18—**Office Management of Chronic Pain.** Maui, Hawaii. Saturday-Saturday. U/W at Wailea Beach, Wailea, Maui, Hawaii. Contact: U/W School of Medicine.

April 11-18—**Drug Therapy.** Maui, Hawaii. Saturday-Saturday. U/W at Royal Lahaina, Maui, Hawaii. Contact: U/W School of Medicine.

April 14—**Pediatric Psychiatry—Univ. of Wash. Pediatrics Sessions** (Spokane). Tuesday. 12-1 p.m., Sacred Heart Medical Center. Contact: Frank Reynolds, MD, WAMI Office, 3 North, Sacred Heart Medical Center, Spokane, WA 99204. (509) 455-8220.

April 18-25—**Emergency Medical Care.** Maui, Hawaii. Saturday-Saturday. U/W at Wailea Beach, Maui, Hawaii. Contact: U/W School of Medicine.

April 27—**Total Parenteral Nutrition—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

April 30-May 2—**Trauma.** Seattle. Thursday-Saturday. Contact: U/W School of Medicine.

May 1—**Management of Acute Medical Problems.** Seattle. Friday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

May 7-8—**Medical Genetics and Teratology.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

May 8-9—**Washington Academy of Family Physicians Annual Scientific Program.** Yakima. Friday-Saturday. Yakima Convention Center. Contact: Carolyn Palmer, 3700 140th Avenue NE, Bellevue, WA 98005. (206) 883-8852.

May 15-16—**Medical Applications of Real-Time Ultrasound.** Seattle. Friday-Saturday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

May 15—**Medical Alumni.** Seattle. Friday. Contact: U/W School of Medicine.

May 18—**Arrhythmias—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

May 19—**Evaluation and Treatment of Premature Labor—Univ. of Wash. OB/GYN Sessions.** (Spokane). Tuesday. 12-1 p.m., Sacred Heart Medical Center. Contact: Wm. Harvey Frazier, MD, West 101 8th Ave., Spokane, WA 99204. (509) 838-8347.

May 21-22—**Critically Ill Surgical Patient.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

May 22-23—**Northwest Academy of Otolaryngology and Head and Neck Surgery Annual Scientific Program.** Seattle. Friday-Saturday. Washington Athletic Club. Contact: C. Thomas Yarington, MD, The Mason Clinic, 1100 Ninth Avenue, Seattle, WA 98101. (206) 223-6833.

May 22-24—**Comprehensive Care for Physically Disabled Children.** Seattle. Friday-Sunday. Washington Plaza. Contact: John A. Hinckley, AACPDM, PO Box 11083, Richmond, VA 23230. (804) 355-0147.

May 23-30—**Allergy and Immunology.** Maui, Hawaii. Saturday-Saturday. U/W at Wailea Beach, Maui, Hawaii. Contact: U/W School of Medicine.

June 4-6—**Radiology Northwest V.** Seattle. Thursday-Saturday. Contact: U/W School of Medicine.

June 4-5—**Pacific Northwest Chapter of the American College of Chest Physicians: Cardiopulmonary Symposium.** Seattle. Thursday-Friday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

June 9—**Pediatric Allergy—Univ. of Wash. Pediatrics Sessions** (Spokane). Tuesday. 12-1 p.m., Sacred Heart Medical Center. Contact: Frank Reynolds, MD, WAMI Office, 3 North, Sacred Heart Medical Center, Spokane, WA 99204. (509) 455-8220.

June 11-12—**Regional Anesthesia and Nerve Block.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

June 15-19—**Death Investigation.** Seattle. Monday-Friday. Contact: U/W School of Medicine.

June 18-19—**Respiratory Care.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

June 18-20—**Modern Office Procedures: Minor Surgeries.** Seattle. Thursday-Saturday. Contact: U/W School of Medicine.

June 22—**Ophthalmology for the Internist—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

July 19-27—**Alaska Cruise: OB/GYN.** Sunday-Monday. Contact: U/W School of Medicine.

July 25-26—**Washington State Society of Anesthesiologists: Seafair III Anesthesia Meeting.** Seattle. Saturday-Sunday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

August 5-7—**Great Debates in Otolaryngology.** Seattle. Wednesday-Friday. Contact: U/W School of Medicine.

August 21-28—**Alaska Cruise: Radiology.** Friday-Friday. Contact: U/W School of Medicine.

August 21-28—**Alaska Cruise: Strabismus.** Friday-Friday. Contact: U/W School of Medicine.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the Academy for Continuing Medical Education, a foundation of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Academy for Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the Academy at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the Academy for current details.

(Continued on Page 47)

Practice what we teach.

Today there are over 31 million men, women and children suffering from the many forms of arthritis and related rheumatic diseases. And there just aren't enough trained rheumatologists to help them.

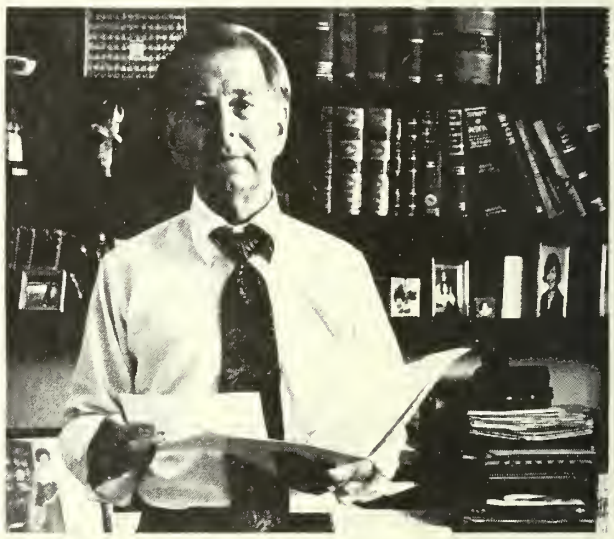
That's why arthritis sufferers need your help.

They must depend heavily on the family practitioner for better diagnosis, more effective patient treatment.

Contact your local Arthritis Foundation chapter for the latest information on arthritis. This includes continuing educational seminars by leading rheumatologists, scientific meetings, "outreach" programs—as well as the "Bulletin on the Rheumatic Diseases," "Arthritis and Rheumatism Journal," "Primer on the Rheumatic Diseases," audio cassettes and other professional materials. Free disease handbooks and medication pamphlets are also available to patients.

Please. Let us help your practice with what we teach.

The Arthritis Foundation helps doctors help.



ARTHRITIS FOUNDATION

A public service of this magazine

(Continued from Page 45)

GRAND ROUNDS

SPONSOR: Primary Children's Medical Center
TITLE: **Pediatric Grand Rounds**
LOCATION: PCMC
DATE: First and third Thursdays—8:00 a.m.
CONTACT: Cathy Van Komen (801) 363-1221
SPONSOR: Utah Valley Hospital, Provo
TITLE: **Interdepartmental Grand Rounds**
LOCATION: UVH
CONTACT: Gary Watts, MD (801) 373-7850 (Ext. 2143)

* * *

February 15-20
SPONSOR: University of Utah
TITLE: **Update on Clinical Microbiology and Immunology**
LOCATION: Park City
FEE: To be announced
CREDIT: 24 hours
CONTACT: John M. Matsen, MD (801) 581-5514

February 17-20
SPONSOR: Primary Children's Medical Center
TITLE: **Postgraduate Course in Pediatric Surgery**
LOCATION: Park City
FEE: $250.00
CREDIT: 12 hours
CONTACT: Stan Everett (801) 350-1100

February 20-24
SPONSOR: University of Utah
TITLE: **26th Annual Postgrad Course in Anesthesiology**
LOCATION: Hotel Utah, Salt Lake City
FEE: To be announced
CREDIT: 16 hours
CONTACT: Theodore H. Stanley, MD (801) 581-6393

February 21-24
SPONSOR: University of Utah
TITLE: **22nd Annual OB-BYN Course**
LOCATION: Holiday Inn, Park City
FEE: $250.00
CREDIT: 15 hours
CONTACT: David H. Engelberg, MD (801) 581-7647

February 22-27
SPONSOR: Utah Ophthalmological Society
TITLE: **OUS Winter Meeting**
LOCATION: Park City
FEE: To be announced
CREDIT: 16 hours
CONTACT: A. Thomas Williams, MD (801) 268-6111

February 25-27
SPONSOR: University of Utah/Intermountain Pediatric Society/ American Academy of Pediatrics
TITLE: **Common Problems in Pediatrics III**
LOCATION: Salt Lake Hilton
FEE: $150.00+$15.00 each mini-course
CREDIT: 16 hours
CONTACT: Bruce Buehler, MD (801) 581-7877

February 25-28
SPONSOR: University of Utah
TITLE: **Gynecologic Oncology Course**
LOCATION: Park City
FEE: $250.00, physicians; $150.00, residents, nurses
CREDIT: 15 hours
CONTACT: David H. Engleberg (801) 581-5501

February 25-March 7
SPONSOR: University of Utah
TITLE: **Midwinter Radiology Pacific Cruise Meeting**
LOCATION: Departs from Los Angeles
FEE: $300.00
CREDIT: To be announced
CONTACT: P. Ruben Koehler, MD (801) 581-8818

February 27-28
SPONSOR: LDS Hospital/Dixie Medical Center
TITLE: **Second Annual Dixie Medical Center Symposium**
LOCATION: Hilton Inn, St. George
FEE: To be announced
CREDIT: To be announced
CONTACT: Carlyle F. Stout, MD (801) 673-4642
Warren Stucki, MD (801) 628-1641

February 28-March 7
SPONSOR: University of Utah
TITLE: **6th Annual Advances in Internal Medicine**
LOCATION: Snowbird
FEE: $225.00
CREDIT: 25 hours
CONTACT: Malcolm Berenson, MD (801) 581-7802

February 28-March 7
SPONSOR: University of Utah
TITLE: **Nutrition and Contemporary Medicine**
LOCATION: Park City
FEE: $200.00
CREDIT: 25 hours
CONTACT: Malcolm Berenson, MD (801) 581-7802

March 6
SPONSOR: University of Utah, Dept. of Internal Medicine
TITLE: **Infectious Disease**
LOCATION: UUMC
FEE: None
CREDIT: 2 hours
CONTACT: Malcolm Berenson, MD (801) 581-7803

March 7-14
SPONSOR: University of Utah
TITLE: **Medical and Surgical Advances in Gastroenterology**
LOCATION: Snowbird
FEE: To be announced
CREDIT: 25 hours
CONTACT: Malcolm Berenson, MD (801) 581-7802

SPONSORS OF COURSES—ABBREVIATIONS

AF: Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.
CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.
CWH: Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461
FHP: Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.
HAFB: Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.
LDSH: Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.
MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.
OEH: Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.
OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409
PCMC: Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.
SHCC: Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.
SLSC: Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.
UAFP: Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.
UUMC: University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.
UVH: Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.
VAMC: Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—4107 Laurel St., Anchorage 99504. Annual Meeting: May 23-27, 1981, Glacier Bay Lodge, Glacier Bay.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. Annual Meeting: April 22-26, 1981, The Pointe Resort, Phoenix.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: March 13-18, 1981, Disneyland Hotel, Anaheim.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. Annual Meeting: September 9-12, 1981, Keystone.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. Annual Meeting: October 12-16, 1981, Ilikai Hotel, Honolulu.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. Annual Meeting: July 23-26, 1981, Sun Valley.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Interim Meeting: April 10-11, 1981, Colonial Inn, Helena. Annual Meeting: October 1-3, 1981, Copper King Inn, Butte.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. Annual Meeting: May 15-17, 1981, Carson City.

New Mexico Medical Society—2650 Yale SE, Albuquerque 87106. Annual Meeting: May 6-8, 1981, Hilton Inn, Albuquerque.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. Annual Scientific Session: October 29-30, 1981, Portland.

Utah State Medical Association—540 East Fifth South St., Salt Lake City 84102. Annual Meeting: September 8-11, 1981, Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. Annual Meeting: September 24-27, 1981, Davenport Hotel, Spokane.

Wyoming State Medical Society—P.O. Drawer 4009, Cheyenne 82001. Annual Meeting: June 22-26, 1981, Ramada Snow King Inn, Jackson.

March 14-21

SPONSOR: University of Utah
TITLE: **3rd Annual Park City Radiology Conference: Neuroradiology**
LOCATION: Park City
FEE: $240.00
CREDIT: To be announced
CONTACT: P. Ruben Koehler, MD (801) 581-8818

April 1

SPONSOR: University of Utah, Dept. of Internal Medicine
TITLE: **Clinical Pharmacology**
LOCATION: UUMC
FEE: None
CREDIT: 2 hours
CONTACT: Malcolm Berenson, MD (801) 581-7803

April 8-10

SPONSOR: University of Utah Rocky Mountain Center for Occupational and Environmental Health/ University of Arizona Center for Occupational Safety and Health/University of Texas Health Science Center, School of Public Health
TITLE: **3rd Annual Park City Environmental Health Conference: Legal and Ethical Dilemmas in Occupational Health**
LOCATION: Prospector Square Lodge, Park City
FEE: Advance registration, $195.00; after March 13, $250.00
CREDIT: 20.5 hours
CONTACT: Katharine Blosch (801) 581-5710

April 17

SPONSOR: Academy for Continuing Medical Education
TITLE: **First Intermountain Conference on CME**
LOCATION: TriArc Travel Lodge, Salt Lake City
FEE: $50.00 (attendance limited to 100)
CREDIT: 7 hours (certified by University of Utah College of Medicine)
CONTACT: Pam Hanson, ACME (801) 355-5290

June 22-25

SPONSOR: University of Utah
TITLE: **Alcoholism and Other Drug Dependencies**
LOCATION: University Medical Center, Classroom C
FEE: To be announced
CREDIT: 28 hours
CONTACT: James R. Swenson, MD (801) 581-7985

Note: Dates, times, places and programs are subject to change on occasion. Please check with the sponsoring organization or the Academy for details.

Index to
The Western Journal of Medicine Advertising

AYERST LABORATORIES
Premarin 24, 25, 26

BANK OF AMERICA
Business Services 33

BANKER INVESTMENT COMPANY/SECURITY PACIFIC FINANCE CORP. 43

BRIG COMPUTERS AND SOFTWARE 5

BRISTOL LABORATORIES
Tegopen 34, 35, 36

BURROUGHS WELLCOME CO.
Zyloprim 2

CLASSIFIED 15, 16, 37, 38

DOCTORS' CO., THE 6

ELI LILLY AND COMPANY
Ceclor 3

HCP CONDO RESORTS 30

HELIOSYSTEMS 9

HOSPITAL OF THE GOOD SAMARITAN, THE
Ovarian Cancer Symposium 38

NORCAL MUTUAL INSURANCE CO. 11

PUREPAC PHARMACEUTICAL CO. 17

ROCHE LABORATORIES
Corporate 10
Dalmane ..... 2nd Cover, 1, 2
Libitrol ..... 3rd and 4th covers
Trimpex 28, 29, 30

SMITH KLINE & FRENCH CO.
Dyazide 32
Physician Recruitment 36

E. R. SQUIBB & SONS INC.
Corgard 19, 20, 21, 22

UNIVERSITY OF CALIFORNIA, RIVERSIDE
3rd Annual Nicholas Institute Symposium 43

WESTERN JOURNAL OF MEDICINE, THE
Subscription 31

WYETH LABORATORIES
Lo/Ovral 12, 13, 14

THE WESTERN Journal of Medicine

VOLUME 134 • NUMBER 3 **MARCH 1981**

193 *The Hemolytic-Uremic Syndrome* CRAIG BRASHER, MD, and RICHARD L. SIEGLER, MD

198 *Fine-Needle Aspiration Biopsy in the Management of Thyroid Nodules*
THEODORE R. MILLER, MD; JOHN S. ABELE, MD, and FRANCIS S. GREENSPAN, MD

206 *Penile Revascularization in the Treatment of Impotence* IRA D. SHARLIP, MD

CASE REPORTS

212 *Bronchogenic Cyst Presenting Subsequent to Intrapleural Rupture*
CARLOS A. SCHMIDT, MD; ROBERT GORDON, MD, and CHANGWOO AHN, MD

215 *Lightning Burns* VIRGINIA L. McCRADY-KAHN, RN, BSN, and ARTHUR M. KAHN, MD

220 *Unilateral Hydrothorax Secondary to Ascites—Demonstration by a Noninvasive Radionuclide Imaging Technique* KOKILA VYAS, MD, and GERBAIL T. KRISHNAMURTHY, MD

MEDICAL PROGRESS

223 *Psychopharmacology in Medical Practice—The Benefits and the Risks*
ROBERT L. SACK, MD, and JAMES H. SHORE, MD

SPECIALTY CONFERENCE

234 *Thrombosis: Its Role and Prevention in Cardiovascular Events—Part I*
Participants: LAURENCE A. HARKER, MD; ARTHUR R. THOMPSON, MD, PhD, and JOHN M. HARLAN, MD

MEDICAL STAFF CONFERENCE

242 *Aortoenteric Fistula* Chief Discussant: LAWRENCE M. TIERNEY, Jr, MD

IMPORTANT ADVANCES IN CLINICAL MEDICINE

248 *Radiology—Epitomes of Progress*

EDITORIALS

258 • *Of Gerontology, Geriatrics and Gereology* • *Psychotherapeutic Drugs in Medical Practice* • *Customer Satisfaction* • *The Platelet Connection in Arteriosclerotic Disease*

CORRESPONDENCE

263 • *Relapsing Fever Revisited* • *Coronary Bypass Operations* • *Problems Associated With Megadose Vitamin C Therapy* • *Health Care Rules and Regulations* • *Appropriateness Review: An Overview*

MEDICINE IN PERSPECTIVE

267 *An American Physician in Rural West Africa* WILLIAM L. MINKOWSKI, MD, MPH

INFORMATION

273 *Xeromammography Versus Screen-Film Mammography—Pros and Cons of the Two Techniques*
EDWARD A. SICKLES, MD

274 *Advances in Burn Care* DAVID M. HEIMBACH, MD; LOREN H. ENGRAV, MD and JANET A. MARVIN, RN, MN

280 *Articles to Read in Other Journals*

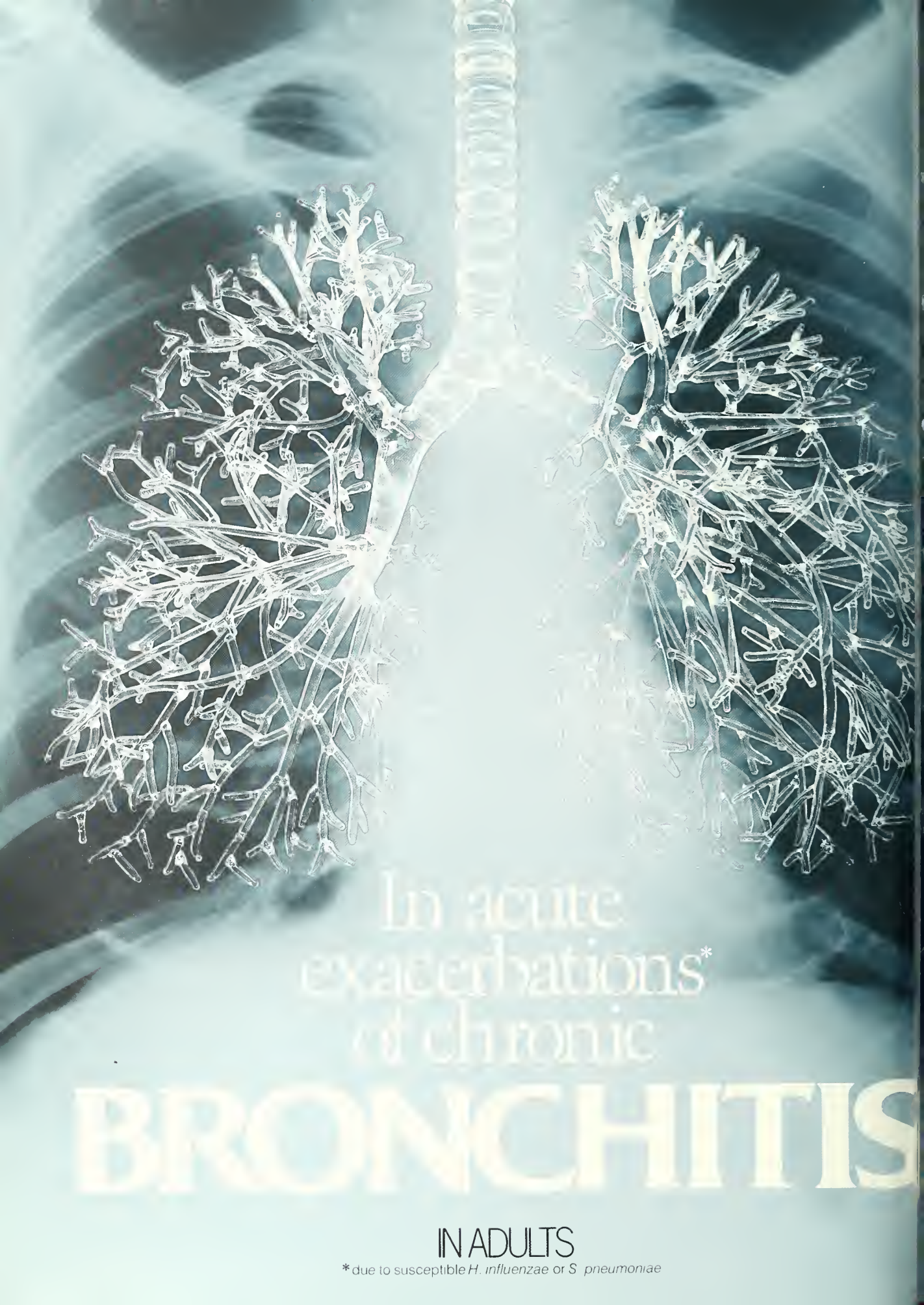
281 *In Memoriam*

Detailed Table of Contents, See Advertising Pages 6 and 12

Information for Authors, See January Issue, Advertising Page 10

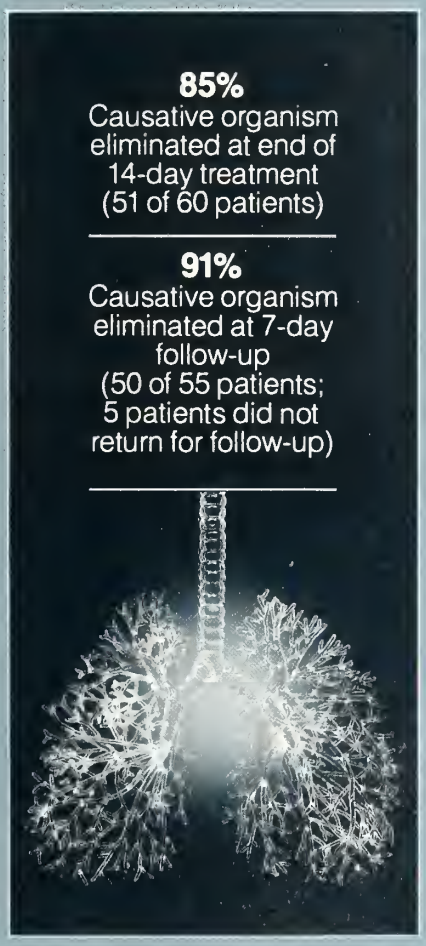
★ **CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA, HAWAII AND NEVADA: ALASKA, MONTANA AND IDAHO; NEW MEXICO; OREGON; WASHINGTON; UTAH**
(See Advertising Page 17)

★★ **Official Journal of the California Medical Association, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association and the Washington State Medical Association**


In acute
exacerbations*
of chronic
BRONCHITIS
IN ADULTS
*due to susceptible H. influenzae or S. pneumoniae

91%
verall success
rate 7 days
posttherapy
n controlled
multicenter
studies
involving
influenzae &
pneumoniae†

ROCHE



☐ Low incidence of diarrhea and bronchial superinfection.

☐ Gastrointestinal and dermatological reactions were the most frequent side effects in the study.

☐ May be used in patients allergic to penicillins and cephalosporins.

☐ Convenient b.i.d. dosage encourages compliance.

☐ During therapy, maintain adequate fluid intake. Use cautiously in patients with impaired renal or hepatic function, severe allergy or bronchial asthma.

Bactrim is indicated in acute exacerbations of chronic bronchitis in adults when in the physician's judgment it offers an advantage over a single antimicrobial agent.

†Data on file, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

BACTRIM™ DS

ch tablet contains 160 mg trimethoprim and 800 mg sulfamethoxazole.

Please see next page for summary of product information.

BACTRIM™

ROCHE

(trimethoprim and sulfamethoxazole)

A MAJOR ANTIMICROBIAL WITH MULTI-SYSTEM USEFULNESS

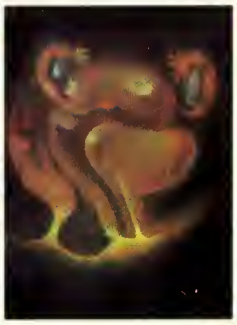
The clinical usefulness of Bactrim continues to grow. Now Bactrim is useful for all of the following infections when due to susceptible strains of indicated organisms (see indications section in summary of product information):

UPPER RESPIRATORY

acute otitis media in children

LOWER RESPIRATORY

acute exacerbations of chronic bronchitis in adults —documented *Pneumocystis carinii* pneumonitis



GENITO-URINARY

recurrent urinary tract infections

GASTRO-INTESTINAL

shigellosis

Before prescribing, please consult complete product information, summary of which follows:

Indications and Usage: For the treatment of urinary tract infectio to susceptible strains of the following organisms: *Escherichio coli, Klebsiella-Enterobacter, Proteus mirubilis, Proteus vulgaris, Proteu gonii*. It is recommended that initial episodes of uncomplicated ur tract infections be treated with a single effective antibacterial age rather than the combination. *Note:* The increasing frequency of resista organisms limits the usefulness of all antibacterials, especially in these urina tract infections.

For acute otitis media in children due to susceptible strains of *Hoemophilus influenzoe* or *Streptococcus pneumonioe* when in phy cian's judgment it offers an advantage over other antimicrobials. I clinical information presently available on effectiveness of treatm otitis media with Bactrim when infection is due to ampicillin-resis *Hoemophilus influenzae*. To date, there are limited data on the saf repeated use of Bactrim in children under two years of age. Bactri not indicated for prophylactic or prolonged administration in otiti at any age.

For acute exacerbations of chronic bronchitis in adults due to sus ble strains of *Hoemophilus influenzae* or *Streptococcus pneumonic* when in physician's judgment it offers an advantage over a single timicrobial agent.

For enteritis due to susceptible strains of *Shigella flexneri* and *Shi sonnei* when antibacterial therapy is indicated.

Also for the treatment of documented *Pneumocystis carinii* pneum To date, this drug has been tested only in patients 9 months to 16 of age who were immunosuppressed by cancer therapy.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides; pre nursing mothers; infants less than two months of age.

Warnings: BACTRIM SHOULD NOT BE USED TO TREAT STREPTOC PHARYNGITIS. Clinical studies show that patients with group A β-hemolyti tococcal tonsillopharyngitis have higher incidence of bacteriologic failure whe treated with Bactrim than do those treated with penicillin. Deaths from hype sitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias been associated with sulfonamides. Experience with trimethoprim is much n limited but occasional interference with hematopoiesis has been reported a an increased incidence of thrombopenia with purpura in elderly patients on diuretics, primarily thiazides. Sore throat, fever, pallor, purpura or jaundice early signs of serious blood disorders. Frequent CBC's are recommended; t should he discontinued if a significantly reduced count of any for blood element is noted.

Precautions: Use cautiously in patients with impaired renal or l function, possible folate deficiency, severe allergy or bronchial a patients with glucose-6-phosphate dehydrogenase deficiency, her frequently dose-related, may occur. During therapy, maintain ade fluid intake and perform frequent urinalyses, with careful micros examination, and renal function tests, particularly where there is paired renal function. Bactrim may prolong prothrombin time in t receiving warfarin; reassess coagulation time when administering to these patients.

Adverse Reactions: All major reactions to sulfonamides and tri prim are included, even if not reported with Bactrim. *Blood dyscr* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombo leukopenia, hemolytic anemia, purpura, hypoprothrombinemia an methemoglobinemia. *Allergic reactions:* Erythema multiforme, Ste Johnson syndrome, generalized skin eruptions, epidermal necrol ticaria, serum sickness, pruritus, exfoliative dermatitis, anaphyla reactions, periorbital edema, conjunctival and scleral injection, p sensitization, arthralgia and allergic myocarditis. *Gastrointestinal reactions:* stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancre *CNS reactions:* Headache, peripheral neuritis, mental depression, convulsion ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle we and nervousness. *Miscelloneous reactions:* Drug fever, chills, toxic nephrosi oliguria and anuria, periarteritis nodosa and L.E. phenomenon. Due to certa chemical similarities to some goitrogens, diuretics (acetazolamide, thiazide oral hypoglycemic agents, sulfonamides have caused rare instances of goiter tion, diuresis and hypoglycemia in patients; cross-sensitivity with these agen exist. In rats, long-term therapy with sulfonamides has produced thyroid ma.

Dosage: Not recommended for infants less than two months of ag

URINARY TRACT INFECTIONS AND SHIGELLOSIS IN ADULTS AND CHILDREN. ACUTE OTITIS MEDIA IN CHILDREN

Adults: Usual adult dosage for urinary tract infections—1 D5 tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 10-14 days. identical daily dosage for 5 days for shigellosis.

Children: Recommended dosage for children with urinary tract infections or otitis media—8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24. in two divided doses for 10 days. Use identical daily dosage for 5 days for shi

For patients with renol impoirment: Use recommended dosage regimen whe creatinine clearance is above 30 ml/min. If creatinine clearance is between ml/min, use one-half the usual regimen. Bactrim is not recommended if cre clearance is below 15 ml/min.

ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS IN ADULTS:

Usuol odult dosage: 1 D5 tablet (double strength), 2 tablets (single strength 4 teasp. (20 ml) b.i.d. for 14 days.

PNEUMOCYSTIS CARINII PNEUMONITIS:

Recommended dosage: 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxa 24 hours in equal doses every 6 hours for 14 days. See complete product inf for suggested children's dosage table.

Supplied: *Double Strength (DS) toblets,* each containing 160 mg trimethopri 800 mg sulfamethoxazole, bottles of 100; Tel-E-Dose® packages of 100; Presc Paks of 20 and 28. *Toblets,* each containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 100 and 500; Tel-E-Dose® packages of 100; Pre Paks of 40. *Pediotric Suspension,* containing in each teaspoonful (5 ml) the of 40 mg trimethoprim and 200 mg sulfamethoxazole; cherry flavored—bottl 16 oz (1 pint). *Suspension,* containing in each teaspoonful (5 ml) the equivale 40 mg trimethoprim and 200 mg sulfamethoxazole, fruit-licorice flavored—b 16 oz (1 pint).

ROCHE

ROCHE LABORATORIES
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

works well in your office...

NEOSPORIN® Ointment

(polymyxin B-bacitracin-neomycin)

Each gram contains: Aerosporin® (Polymyxin B Sulfate) 5,000 units, bacitracin zinc 400 units, neomycin sulfate 5 mg (equivalent to 3.5 mg neomycin base); special white petrolatum qs; in tubes of 1 oz and 1/2 oz and 1/32 oz (approx.) foil packets.

works just as well in their homes.

- It's effective therapy for abrasions, lacerations, open wounds, primary pyodermas, secondarily infected dermatoses.
- It provides broad-spectrum overlapping antibacterial effectiveness against common susceptible pathogens, including staph and strep.

- It helps prevent topical infections, and treats those that have already started.
- It contains three antibiotics that are rarely used systemically.
- It is convenient to recommend without a prescription.

NEOSPORIN® Ointment—for the office, for the home.
(polymyxin B-bacitracin-neomycin)

Effective • Economical • Convenient • Recommendable

ch gram contains: Aerosporin® (Polymyxin B Sulfate) 00 units, bacitracin zinc 400 units, neomycin sulfate ng (equivalent to 3.5 mg neomycin base); special white trolatum qs; in tubes of 1 oz and 1/2 oz and 1/32 oz pprox.) foil packets.

ARNING: Because of the potential hazard of nephro-xicity and ototoxicity due to neomycin, care should be ercised when using this product in treating extensive urns, trophic ulceration and other extensive conditions here absorption of neomycin is possible. In burns here more than 20 percent of the body surface is fected, especially if the patient has impaired renal nction or is receiving other aminoglycoside anti-otics concurrently, not more than one application a y is recommended.

When using neomycin-containing products to control secondary infection in the chronic dermatoses, it should be borne in mind that the skin is more liable to become sensitized to many substances, including neomycin. The manifestation of sensitization to neomycin is usually a low grade reddening with swelling, dry scaling and itching; it may be manifest simply as a failure to heal. During long-term use of neomycin-containing products, periodic examination for such signs is advisable and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for that patient thereafter.

PRECAUTIONS: As with other antibacterial preparations, prolonged use may result in overgrowth of non-susceptible organisms, including fungi. Appropriate measures should be taken if this occurs.

ADVERSE REACTIONS: Neomycin is a not uncommon cutaneous sensitizer. Articles in the current literature indicate an increase in the prevalence of persons allergic to neomycin. Ototoxicity and nephrotoxicity have been reported (see Warning section).

Complete literature available on request from Professional Services Dept. PML.

Wellcome / **Burroughs Wellcome Co.**
Research Triangle Park
North Carolina 27709

THE WESTERN Journal of Medicine

Since 1902 (ISSN 0093-0415)

731 MARKET ST. • SAN FRANCISCO, CA 94103 • TELEPHONE (415) 777-2000

Official Journal of the California Medical Association, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association and the Washington State Medical Association

MALCOLM S. M. WATTS, MD, *Editor*
LLOYD H. SMITH, JR., MD, *Associate Editor*
DAVID GREER, *Managing Editor*
BARBARA T. ROONEY, *Assistant Managing Editor*

editorial communications to:
MALCOLM S. M. WATTS, MD, *Editor*

business communications to:
DAVID GREER, *Managing Editor*

MARY KAY COWANS
Advertising Production Manager

Editorial Board

Chairman of the Board
Malcolm S. M. Watts, San Francisco, Ca

Special Editor for Idaho
E. R. W. Fox, Coeur d'Alene, Id

Special Editor for Nevada
Thomas J. Scully, Reno, Nv

Special Editor for New Mexico
Marcus J. Smith, Santa Fe, NM

Special Editor for Utah
John H. Holbrook, Salt Lake City, Ut

Special Editor for Washington
David Hopkins, Federal Way, Wa

Allergy
Harold S. Novey, Orange, Ca
Abba I. Terr, San Francisco, Ca

Anesthesiology
Ronald L. Katz, Los Angeles, Ca

Cardiac and Thoracic Surgery
John E. Connolly, Irvine, Ca
Albert Starr, Portland, Or

Chest Diseases
Roger K. Larson, Fresno, Ca
Thomas L. Petty, Denver, Co

Dermatology
John H. Epstein, San Francisco, Ca
George F. Odland, Seattle, Wa
Richard B. Stoughton, San Diego, Ca

General and Family Practice
Daniel D. Roberts, Central Point, Or
Harmon E. Holverson, Emmett, Id
Wilfred Snodgrass, Santa Monica, Ca

General Surgery
Fred M. Anderson, Reno, Nv
Daniel T. Cloud, Phoenix, Az
Paul A. Ebert, San Francisco, Ca
Lucius D. Hill, Seattle, Wa
Frank G. Moody, Salt Lake City, Ut

Industrial Medicine and Toxicology
Thomas H. Milby, Berkeley, Ca

Internal Medicine
Robert W. Burrough, Spokane, Wa
Theodore C. Eickhoff, Denver Co
Robert L. Hare, Portland, Or
Robert H. Moser, Philadelphia, Pa
George A. Porter, Portland, Or
Helen M. Ranney, San Diego, Ca
David D. Ulmer, Los Angeles, Ca
Edgar Wayburn, San Francisco, Ca
Ralph C. Williams, Jr., Albuquerque, NM

Neurology
Pierre M. Dreyfus, Sacramento, Ca
Philip D. Swanson, Seattle, Wa
W. C. Wiederholt, La Jolla, Ca

Neurosurgery
John R. Green, Phoenix, Az
Arthur A. Ward, Jr., Seattle, Wa
Charles B. Wilson, San Francisco, Ca

Nuclear Medicine
Joseph P. Kriss, Stanford, Ca

Obstetrics and Gynecology
Ralph C. Benson, Portland, Or
Ralph W. Hale, Honolulu, Hi
W. LeRoy Heinrichs, Stanford, Ca
Morton A. Stenchever, Seattle, Wa

Ophthalmology
Robert S. Hepler, Los Angeles, Ca
Bruce E. Spivey, San Francisco, Ca

Orthopedics
Ernest M. Burgess, Seattle, Wa
Duane M. Kline, Jr., Cheyene, Wy

Otolaryngology
Roger Boles, San Francisco, Ca
Mansfield F. W. Smith, San Jose, Ca

Pathology
Richard L. Kempson, Stanford, Ca

Pediatrics
Louis K. Diamond, San Francisco, Ca
William L. Nyhan, San Diego, Ca
Irving Schulman, Stanford, Ca
Arnold L. Smith, Seattle, Wa

Pharmacology
George N. Aagaard, Seattle, Wa

Physical Medicine and Rehabilitation
Glenn G. Reynolds, San Jose, Ca

Plastic Surgery
Richard P. Jobe, Los Altos, Ca
N. John Wilde, Fresno, Ca

Psychiatry
Carl Eisdorfer, Seattle, Wa
Alan I. Levenson, Tucson, Az
Helen Tausend, Beverly Hills, Ca
Joe Paul Tupin, Sacramento, Ca

Public Health
J. M. Stubblebine, Greenbrae, Ca
Irma M. West, Sacramento, Ca

Radiology
M. Paul Capp, Tucson, Az
Melvin M. Figley, Seattle, Wa
Marshall Rowen, Orange, Ca

Urology
Richard Middleton, Salt Lake City Ut
Thomas A. Stamey, Stanford Ca

Consulting Editor
Medical Services and Health Care
Paul J. Sanazaro, Berkeley, Ca

Policy Committee—Editorial Board

JOSEPH F. BOYLE ..... Los Angeles
BRAD COHN ..... San Francisco
GLADDEN V. ELLIOTT ..... La Mesa
SAMUEL HOROWITZ ..... Los Angeles
ROBERT D. BURNETT ..... Sunnyvale
THEODORE W. LORING ..... Eureka
MALCOLM S. M. WATTS ..... San Francisco

Advertisements—THE WESTERN JOURNAL OF MEDICINE is published the first week of each month. Advertising copy must be received not later than the first of the month preceding issue. Advertising rates will be sent on request. Acceptance of advertising is contingent upon approval by the Advertising Committee. The journal reserves the right to reject any advertisement.

ADVERTISING SALES REPRESENTATIVES:

EAST:
SAUL HORNIK
P.O. BOX 246
MORGANVILLE, NJ 07751
TEL: (201) 462-8004

MIDWEST:
R. C. JOHNSON & ASSOCIATES
RICHARD C. JOHNSON
547 WEST MELROSE
CHICAGO, IL 60657
TEL: (312) 327-6969

WEST:
MEDIA SERVICES
DARIEN DELORENZO
LYNNE JEFFES
2612 BELMONT CANYON RD.
BELMONT, CA 94002
TEL. (415) 595-2203
(415) 348-7478

CLASSIFIED:
731 MARKET ST.
SAN FRANCISCO, CA 94103
TEL. (415) 777-2000
(415) 777-0424

Copyright 1981 by the California Medical Association

Owned and Published by the California Medical Association

All material subject to this copyright appearing in THE WESTERN JOURNAL OF MEDICINE may be photocopied for the noncommercial purpose of scientific or educational advancement. Volumes begin with the first of January and the first of July.

The subscription price per year is $10 in the United States and Canada; $18 in all other countries. Single copies are $2. Address all subscription communications to THE WESTERN JOURNAL OF MEDICINE Circulation, 731 Market St., San Francisco, CA 94103.

Allow six weeks for subscriptions to begin. Past issues must be bought individually. So long as reserve stocks are available, missing issue requests from subscribers are honored for up to six months after the issue date. Thereafter, the single copy rate of $2.00 is applicable for each issue available.

"Change of Address"—Requests for change of address should give both the old and new addresses. Allow six weeks for change-over.

CONTRIBUTIONS OF SCIENTIFIC AND ORIGINAL ARTICLES

Responsibilities for Statements and Conclusions in Original Articles—Authors are responsible for all statements, conclusions and methods of presenting their subjects. These may or may not be in harmony with the views of the editorial staff. It is aimed to permit authors to have as wide latitude as the general policy of the journal and the demands on its space may permit. The right to reduce, revise or reject any manuscript is always reserved.

Exclusive Publication—Articles are accepted for publication on condition that they are contributed solely to this journal. Ordinarily contributors will be notified within 60 days if a manuscript is accepted for publication. Every effort will be made to return unused manuscripts.

Length of Articles—Ordinarily articles should not exceed 3,000 words (approximately five printed pages). Under exceptional circumstances only will articles of over 4,000 words be published.

Manuscripts—Manuscripts should be typewritten and double-spaced, and the *original* typescript plus two copies should be submitted.

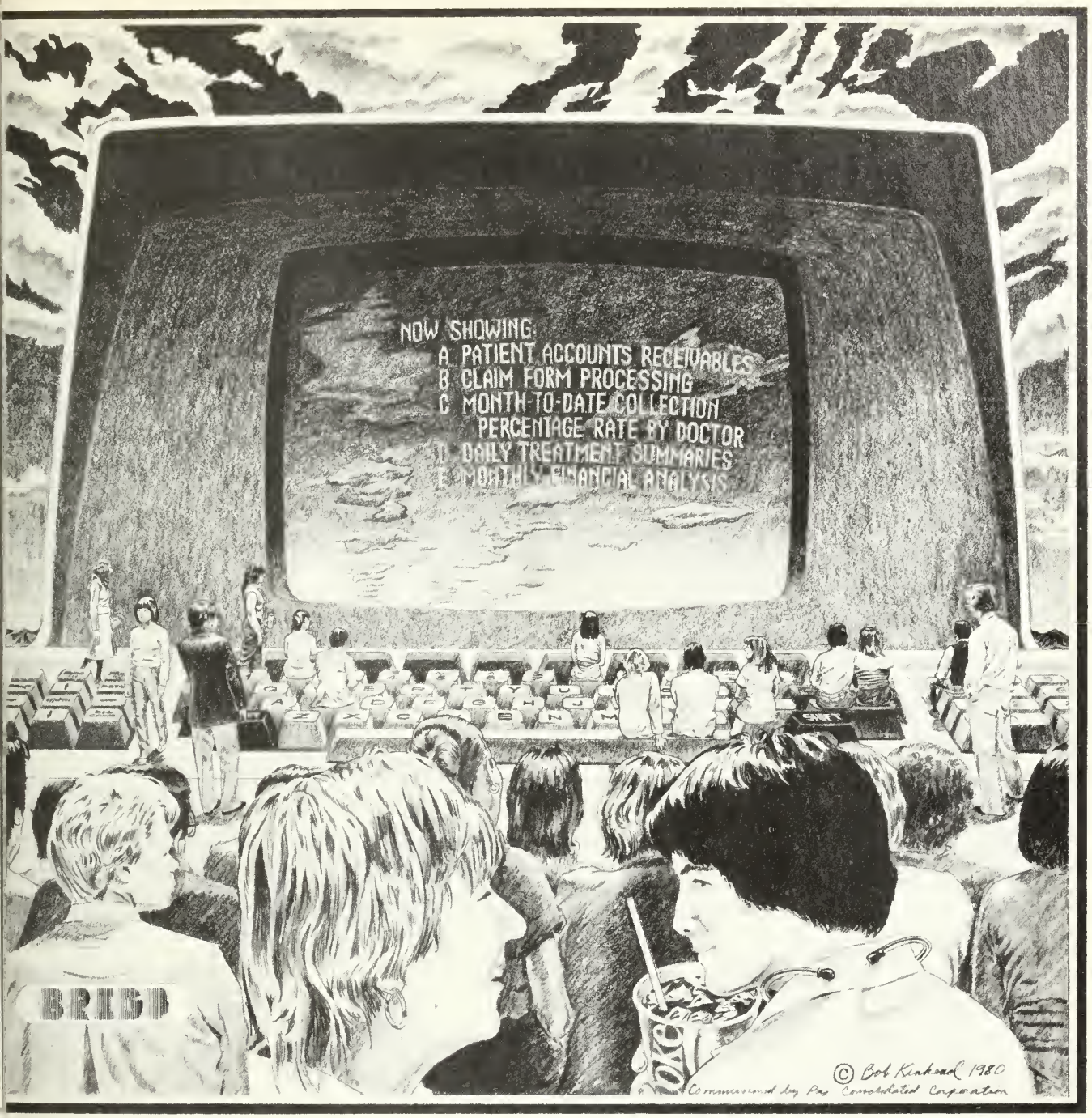
Illustrations—Ordinarily publication of two or three illustrations accompanying an article will be paid for by THE WESTERN JOURNAL OF MEDICINE. Any number beyond this may have to be paid for by the author.

References—References should conform to the following order: name of author, title of article, name of periodical, and volume with inclusive pages, month and year—i.e., Lee GS: The heart rhythm following therapy with digitalis—In theory and practice. Arch Int Med 44:554-562, Dec 1942. They should be listed in the order in which they are cited in the text, numbered in sequence and punctuated as above.

Reprints—Reprints must be paid for by the author at established standard rates.

"Information for Authors" Available on request or see January 1981 issue, advertising page 10.

"Entered as second class matter at the post office in San Francisco under the Act of March 3, 1879." Acceptable for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized August 10, 1918. Publication Number 084480.



Tomorrow's Big Picture.

Today. All of the information you need to operate an ficient, profitable practice comprises the Big Picture.

Daily and monthly financial analysis; summaries by iagnosis, by transaction and by doctor are available at the touch of a nger. And personal statement messages are part of the program.

There's more. Automatic aging. Past due notices. Month-date and year-to-date accounts receivable data with collection rate by doctor. Your Brig Office Management System will process claim forms and statements at a rate of three hundred per hour.

Better still, *your* people can learn to operate the system in a few minutes. For less than the cost of an outside billing service. We have leasing, purchase and rental plans.

Make the necessary decision to automate your office. Call us today for a personal demonstration.

BRIGD

COMPUTERS & SOFTWARE

5830 Uplander Way, Culver City, CA 90230

(213) 641-3297 TWX 910-328-6162 in CA 1 (800) 772-2666 ext. 904 in USA 1 (800) 227-2400 ext. 904

includes Alaska, Hawaii, Puerto Rico and the Virgin Islands

Brig Computers & Software is another division of the world wide services of Pax Consolidated Corporation.

THE WESTERN
Journal of Medicine

VOLUME 134 • NUMBER 3 **MARCH 1981**

TABLE OF CONTENTS

193 *The Hemolytic-Uremic Syndrome* CRAIG BRASHER, MD, and RICHARD L. SIEGLER, MD
From the Division of Pediatric Nephrology, Department of Pediatrics, University of Utah College of Medicine, Salt Lake City.

198 *Fine-Needle Aspiration Biopsy in the Management of Thyroid Nodules*
THEODORE R. MILLER, MD; JOHN S. ABELE, MD, and FRANCIS S. GREENSPAN, MD
From the Departments of Pathology and Medicine, University of California, San Francisco, School of Medicine.

206 *Penile Revascularization in the Treatment of Impotence* IRA D. SHARLIP, MD
Dr. Sharlip is in private practice, as well as with the Department of Urology, University of California, San Francisco, School of Medicine.

CASE REPORTS

212 *Bronchogenic Cyst Presenting Subsequent to Intrapleural Rupture*
CARLOS A. SCHMIDT, MD; ROBERT GORDON, MD, and CHANGWOO AHN, MD
From the Department of Surgery, Southern California Permanente Medical Group, Fontana.

215 *Lightning Burns* VIRGINIA L. McCRADY-KAHN, RN, BSN, and ARTHUR M. KAHN, MD
From the Burn Center, Brotman Medical Center, Culver City, California.

220 *Unilateral Hydrothorax Secondary to Ascites—Demonstration by a Noninvasive Radionuclide Imaging Technique* KOKILA VYAS, MD, and GERBAIL T. KRISHNAMURTHY, MD
From the Nuclear Medicine Service, Veterans Admistration Medical Center, and the Departments of Clinical Pathology and Medicine, University of Oregon Health Sciences Center, Portland.

MEDICAL PROGRESS

223 *Psychopharmacology in Medical Practice—The Benefits and the Risks*
ROBERT L. SACK, MD, and JAMES H. SHORE, MD
From the Department of Psychiatry, University of Oregon Health Sciences Center, Portland.

SPECIALTY CONFERENCE

234 *Thrombosis: Its Role and Prevention in Cardiovascular Events—Part I*
Participants: LAURENCE A. HARKER, MD; ARTHUR R. THOMPSON, MD, PhD, and JOHN M. HARLAN, MD
An edited transcription of a Hematology-Oncology Conference, Department of Medicine, Division of Hematology, University of Washington School of Medicine, Seattle.

MEDICAL STAFF CONFERENCE

242 *Aortoenteric Fistula* Chief Discussant: LAWRENCE M. TIERNEY, Jr, MD
A discussion selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from a transcription, it was prepared by Drs. David W. Martin, Jr, Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine.

IMPORTANT ADVANCES IN CLINICAL MEDICINE

Radiology—Epitomes of Progress
Items of progress in radiology. Each item in the judgment of a panel of knowledgeable physicians has recently become reasonably firmly established, both as to scientific fact and important clinical significance.

248 *Cholescintigraphy: Hepatobiliary Imaging With IDA Derivatives Labeled With Technetium 99m* KATHRYN F. WITZTUM, MD

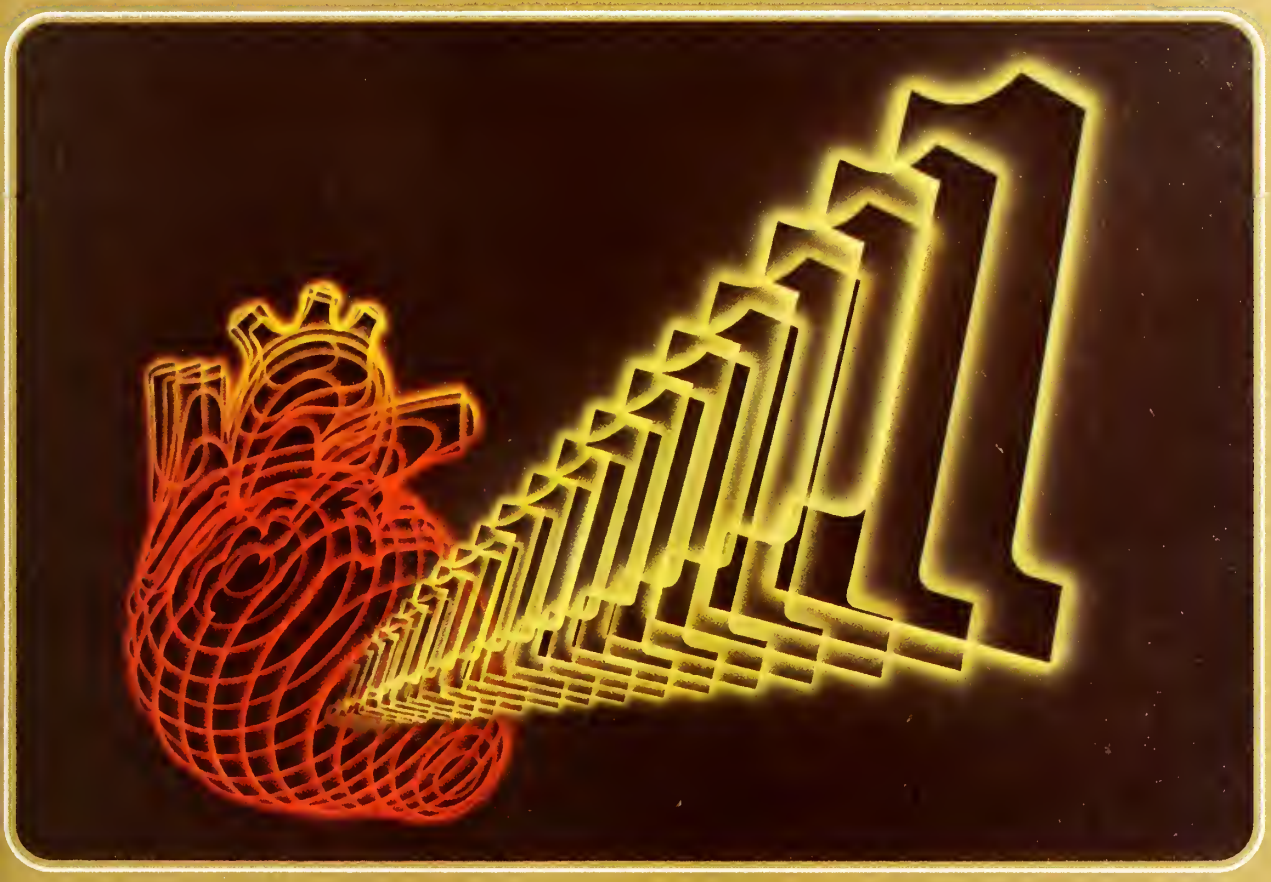
249 *CT Evaluation of Lymphoma* RONALD A. CASTELLINO, MD

250 *CT Evaluation of Pulmonary Metastatic Disease* W. RICHARD WEBB, MD

250 *Ultrasound Scanning in Gallbladder Disease* CHARLES E. FISKE, MD, and ROY A. FILLY, MD

(Continued on page 12)

CORGARD®
nadolol tablets

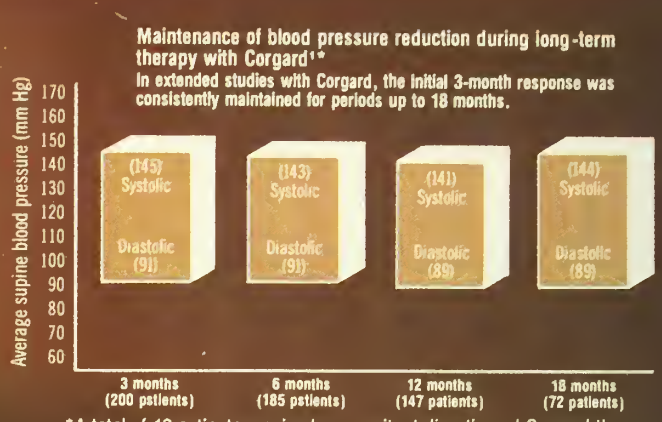


The first beta-blocker with once-a-day dosage

Round-the-clock protection in the control of hypertension

SQUIBB

See last page of this advertisement for brief summary.



*A total of 18 patients received concomitant diuretic and Corgard therapy.

When you prescribe...

CORGARD® [nadolol tablets] ...for significant blood pressure reduction

In short-term clinical studies of 114 patients with mild, moderate and severe hypertension, Corgard taken in single daily doses of 40–320 mg (mean: 200 mg) achieved a significant overall reduction in supine and standing blood pressure in 94% of patients — this included 62.3% of the patients who achieved normalized supine diastolic pressure (≤ 90 mm Hg).

...for comparable efficacy, once a day, to propranolol, four times a day

In a controlled clinical comparison of 179 patients with mild, moderate and severe hypertension, Corgard, once a day, was as effective in reducing supine and standing pressure as propranolol, four times a day.[1]

...for extended protection in control of mild, moderate and severe hypertension

Corgard provides round-the-clock control of hypertension by reducing elevated systolic and diastolic blood pressure — with a single daily dose.

They can comply.

CORGARD® [nadolol tablets] ...promotes compliance with a single daily dose

The 20- to 24-hour serum half-life of Corgard offers round-the-clock reduction in blood pressure with a once-daily dosage. With no need to interrupt daily activities to take multiple doses of medication, patients are more likely to comply.

...is often effective alone, without a diuretic[1]

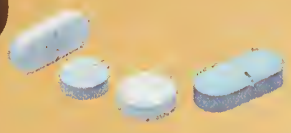
Control of blood pressure with a single agent also simplifies the patient's medication schedule. Only one medication once a day means less likelihood of forgotten or skipped doses.

...rarely causes impotence, loss of libido, orthostatic hypotension*

Because it is virtually free from these undesirable side effects, the patient can function normally, without undue concern.

Prescribe

CORGARD®
nadolol tablets



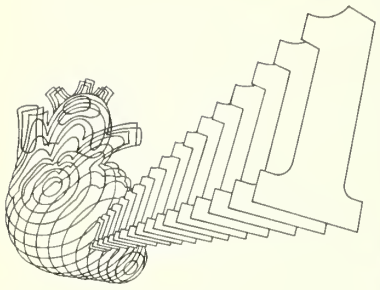
40 mg, 80 mg, 120 mg, and 160 mg tablets

The common-sense beta-blocker for hypertension

SQUIBB®

*Please see brief summary for discussion of Contraindications, Adverse Reactions, Precautions, and Warnings, including avoidance of abrupt withdrawal, on next page of this advertisement.

The only once-a-day beta-blocker for both hypertension and angina pectoris



CORGARD®
nadolol tablets
40 mg, 80 mg, 120 mg, 160 mg scored tablets

CORGARD® TABLETS
Nadolol Tablets

DESCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery — Because beta-blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** — Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory** — Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** — Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System** — reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal** — mesenteric arterial thrombosis; ischemic colitis. **Hematologic** — agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic** — fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous** — reversible alopecia; Peyronie's disease; erythematous rash.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm — Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to 1 mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval — see package insert for dosage in these patients.

For full prescribing information, consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and 1000 tablets and in Unimatic® single-dose packs of 100 tablets.

Reference:
1. Data on file, Squibb Institute for Medical Research.

SQUIBB®

©1981 E.R. Squibb & Sons, Inc.

Issued: January 1981

What they didn't teach you in medical school.

They should have taught Billing along with Biology and Biochemistry.

Because that's the area where many professional practices are hurting. Maybe your practice has classic symptoms – delays, delinquencies, cash flow problems.

But not to worry. Bank of America has an antidote. Our Professional Practice Management Service (PPM).

PPM is a computerized billing system that compiles, processes, stuffs and mails your statements in a fraction of the time it now takes manually.

We offer three flexible input methods designed to meet the needs of your particular practice: personalized; hand-written Account Entry Forms; computer terminals that let you key input directly from your office; or our innovative Audio Response feature where you talk to the computer using your push-button telephone as a terminal.

PPM also automatically prepares insurance forms. Which means we can relieve you of extra processing burdens brought on by new Medi-Cal requirements.

And PPM can give you daily reports listing the status of your accounts, while providing automatic bookkeeping and posting services.

Quite simply, PPM can save you time and money. We know because we've been serving the California health care industry for over 15 years. Currently, more than 1000 professionals use our Professional Practice Management Service.

And it costs less than what you might expect. After all, we're specialists in our field, as you are in yours.

So if you're suffering from acute billing problems, call us in the morning for more information.

It could be all it takes to make your practice perfect.

BANK OF AMERICA

Corporate Electronic Banking

For more information about Bank of America's Professional Practice Management, call: Mike Wisber (415) 622-7368 or Dan DeMarco (213) 683-3742. Or mail this coupon to Bank of America, Corporate Electronic Banking, #3123, P.O. Box 37000, San Francisco, California 94137.

Name_____

Medical Offices_____

Street_____

City/State/Zip_____

Bank of America NT&SA • Member FDIC

(Continued from Page 6)

251 *Therapeutic Angiography* ANTOINETTE S. GOMES, MD

251 *Mammography: Who Needs a Mammogram?* EDWARD A. SICKLES, MD

252 *Applications of CT Scanning in Orthopedics*
LAWRENCE W. BASSETT, MD and ANTHONY A. MANCUSO, MD

253 *Thallium 201 Myocardial Imaging* KENNETH GERBER, MD

254 *Computed Tomography of the Spine and Spinal Contents*
ANTON N. HASSO, MD, and P. E. BILLIMORIA, MD

255 *Metrizamide Myelography* JOHN R. BENTSON, MD

255 *Percutaneous Transhepatic Biliary Drainage* HARVEY ROSENKRANTZ, MD

256 *Contemporary Treatment for Early Breast Cancer*
JEROME STUHLBARG, MD; THOMAS G. SIMKO, MD, and KENNETH M. TOKITA, MD

EDITORIALS

258 *Of Gerontology, Geriatrics and Gereology*

259 *Psychotherapeutic Drugs in Medical Practice* LEO E. HOLLISTER, MD
From the Veterans Administration Medical Center, Palo Alto, California.

261 *Customer Satisfaction*

261 *The Platelet Connection in Arteriosclerotic Disease* ARTHUR J. MOSS, MD
From the Departments of Medicine and Preventive, Family and Rehabilitation Medicine, University of Rochester School of Medicine and Dentistry, Rochester, New York.

CORRESPONDENCE

263 *Relapsing Fever Revisited* STEPHAN D. FIHN, MD, and ERIC B. LARSON, MD, MPH

264 *Coronary Bypass Operations* NORMAN H. MELLOR, MD

264 *Problems Associated With Megadose Vitamin C Therapy* TOWIE FONG, MD

Health Care Rules and Regulations

264 JAMES M. MOOREFIELD, MD

265 JOHN M. KENNEY, MD

265 *Appropriateness Review: An Overview* HOWARD L. LANG, MD

MEDICINE IN PERSPECTIVE

267 *An American Physician in Rural West Africa* WILLIAM L. MINKOWSKI, MD, MPH
Dr. Minkowski is now with the Los Angeles County Department of Health Services.

INFORMATION

273 *Xeromammography Versus Screen-Film Mammography—Pros and Cons of the Two Techniques*
EDWARD A. SICKLES, MD
From the Department of Radiology, Mammography Section, University of California, San Francisco, School of Medicine.

274 *Advances in Burn Care* DAVID M. HEIMBACH, MD; LOREN H. ENGRAV, MD and JANET A. MARVIN, RN, MN
From the Department of Surgery, University of Washington Burn and Trauma Centers, University of Washington, Harborview Medical Center, Seattle.

280 *Articles to Read in Other Journals*
Members of the Editorial Board on occasion call attention to articles they consider to be important in other journals. These titles together with a brief assessment of the articles are published for the information of our readers.

281 *In Memoriam*

Information for Authors, See January Issue, Advertising Page 10

★ CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA, HAWAII AND NEVADA: ALASKA MONTANA AND IDAHO; NEW MEXICO; OREGON; WASHINGTON; UTAH
(See Advertising Page 17)

★★ Official Journal of the California Medical Association, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association and the Washington State Medical Association

et **MIMS**™ take care of your paperwork while you and our staff take care of your patients . . . we think everyone vill feel better.

What if

You didn't have to **worry** about:

- Cash Flow Problems
- Delays, Delinquencies
- Compiling, Processing and Stuffing Patient Bills
- Outdated and Inaccurate Reports
- The Burdens of Insurance Forms Processing

Then

You would already have a Heliosystems' Medical Information Management System (**MIMS**™).

Heliosystems offers a complete in-house computerized solution tailored to your specific needs . . . An effective means of lowering costs and increasing efficiency. It frees the physicians and staff from burdensome, repetitive paperwork and routine chores . . . and you'll no longer have to worry about **WHAT IF's** . . .

CALL COLLECT, (408) 946-6450, FOR YOUR "COMPUTER SYSTEM CASE STUDY" AND ADDITIONAL INFORMATION

HELIO SYSTEMS

A Division of Spectrum Management, Inc.
2195 Zanker Rd. • San Jose, CA.

SPOT-RESISTANT ORAL CONTRACEPTION IS HERE!

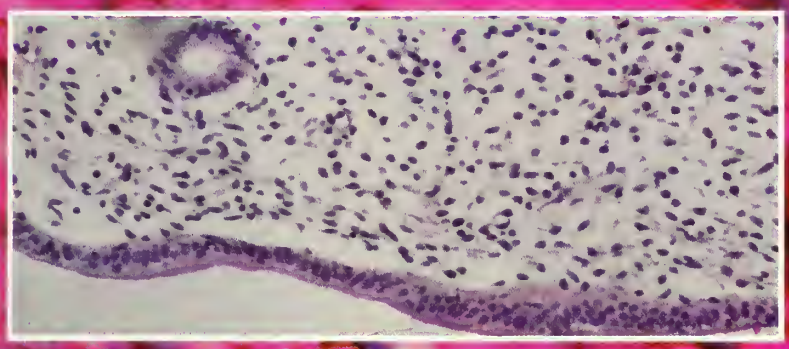
It's LO/OVRAL 30. And here's how it holds spotting and breakthrough bleeding to a minimum: Hormone balance right from the start...and throughout the cycle. Hormone balance made possible with a very low dose oral contraceptive because of the supportive progestational activity of norgestrel, Wyeth's exclusive progestogen.

Regular withdrawal bleeding, too despite its low dose. In clinical trials amenorrhea—defined as absence of bleeding in the 7 pill-free days—was reported in only 2.1% of total cycles. And when defined as absence of bleeding for 60 days or more (as it often is), the incidence was only 0.2%.*

And comfort for most patients* thanks to the same balance that helps prevent spotting and breakthrough bleeding. In the clinical trials, most patients stayed free of common side effects such as nausea (0.6% of cycles), vomiting (0.1%), depression (0.5%) and acne (0.9%).

Wyeth Laboratories
Philadelphia, Pa. 19101

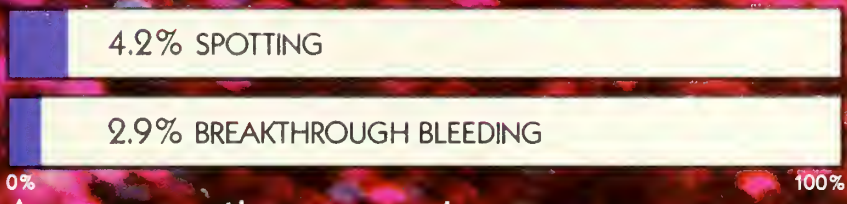
Copyright ©1980, Wyeth Laboratories. All rights reserved.



LO/OVRAL—1st cycle
Biopsy of intact endometrium in stable, progestogen suppressed state. Small, tubular gland in loose stroma without hemorrhage, fragmentation or debris characteristic of desquamating endometrium.

Even in the first cycle, the effective action of LO/OVRAL on the endometrium, such as you see here, provides the resistance against spotting and breakthrough bleeding you hope to achieve.

HISTOLOGICALLY... AND CLINICALLY.



A near-spotless record— in clinical trials involving 22,489 cycles*

*Serious as well as minor adverse reactions have been reported following the use of all oral contraceptives. Contraindications, Warnings, Precautions, Adverse Reactions, etc., in the accompanying In Brief should be carefully considered.

See full prescribing information.

LO/OVRAL® 30 mcg

each tablet contains 0.3 mg norgestrel with 0.03 mg ethinyl estradiol, Wyeth

...with a near-spotless record!

See important information on following page.

IN BRIEF:

Indications and Usage—LO/OVRAL® is indicated for the prevention of pregnancy in women who elect to use oral contraceptives (OC's) as a method of contraception.

Contraindications—OC's should not be used in women with any of the following conditions: 1. Thrombophlebitis or thromboembolic disorders. 2. A past history of deep-vein thrombophlebitis or thromboembolic disorders. 3. Cerebral-vascular or coronary-artery disease. 4. Known or suspected carcinoma of the breast. 5. Known or suspected estrogen-dependent neoplasia. 6. Undiagnosed abnormal genital bleeding. 7. Known or suspected pregnancy (see Warning No. 5). 8. Benign or malignant liver tumor which developed during use of OC's or other estrogen-containing products.

Warnings

Cigarette smoking increases the risk of serious cerdlovasculer side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious conditions, including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks

1. *Thromboembolic Disorders and Other Vascular Problems*—An increased risk of thromboembolic and thrombotic disease associated with use of OC's is well established. Three principal studies in Great Britain and 3 in the U.S. have demonstrated increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic. These studies estimate that users of OC's are 4 to 11 times more likely than nonusers to develop these diseases without evident cause.

CEREBROVASCULAR DISORDERS—In a collaborative American study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than nonusers and the risk of thrombotic stroke was 4 to 9.5 times greater in users than in nonusers.

MYOCARDIAL INFARCTION (MI)—An increased risk of MI associated with use of OC's has been reported, confirming a previously suspected association. These studies, conducted in the UK, found, as expected, that the greater the number of underlying risk factors for coronary artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of pre-eclamptic toxemia) the higher the risk of developing MI, regardless of whether the patient was an OC user or not. OC's, however, were found to be a clear additional risk factor. In terms of relative risk, it has been estimated that OC users who do not smoke (smoking is considered a major predisposing condition to MI) are about twice as likely to have a fatal MI as nonusers who do not smoke. OC users who are also smokers have about a 5-fold increased risk of fatal MI compared to users who do not smoke, but about a 10- to 12-fold increased risk compared to nonusers who do not smoke. Furthermore, amount of smoking is also an important factor. In determining importance of these relative risks, however, baseline rates for various age groups must be given serious consideration. Importance of other predisposing conditions mentioned above in determining relative and absolute risks has not as yet been quantified, quite likely the same synergistic action exists, but perhaps to a lesser extent.

RISK OF DOSE—In an analysis of data derived from several national adverse-reaction reporting systems, British investigators concluded that risk of thromboembolism, including coronary thrombosis, is directly related to dose of estrogen in OC's. Preparations containing 100 mcg or more of estrogen were associated with higher risk of thromboembolism than those containing 50-80 mcg. Their analysis did suggest, however, that quantity of estrogen may not be the sole factor involved. This finding has been confirmed in the U.S.

ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASES—A large prospective study carried out in the UK estimated the mortality rate per 100,000 women per year from diseases of the circulatory system for users and nonusers of OC's according to age, smoking habits, and duration of use. Overall excess death rate annually from circulatory diseases for OC users was estimated to be 20 per 100,000 (ages 15-34—5/100,000, ages 35-44—33/100,000, ages 45-49—140/100,000), risk being concentrated in older women, in those with long duration of use, and in cigarette smokers. It was not possible, however, to examine interrelationships of age, smoking, and duration of use, nor to compare effects of continuous vs. intermittent use. Although the study showed a 10-fold increase in death due to circulatory diseases in users for 5 or more years, all these deaths occurred in women 35 or older. Until larger numbers of women under 35 with continuous use for 5 or more years are available, it is not possible to assess magnitude of relative risk for this younger group. Available data from a variety of sources have been analyzed to estimate risk of death associated with various methods of contraception. Estimates of risk of death for each method include combined risk of contraceptive method (e.g., thromboembolic and thrombotic disease in the case of OC's) plus risk attributable to pregnancy or abortion in event of method failure. This latter risk varies with effectiveness of method. The study concluded that mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of OC's in women over 40 who smoke. Lowest mortality is associated with condom or diaphragm backed up by early abortion. Risk of thromboembolic and thrombotic disease associated with OC's increases with age after about 30 and, for MI, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of pre-eclamptic toxemia, and especially cigarette smoking. Physician and patient should be alert to earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

A 4- to 6-fold increased risk of postsurgery thromboembolic complications has been reported in OC users.

If feasible, OC's should be discontinued at least 4 weeks before surgery of a type associated with increased risk of thromboembolism or prolonged immobilization.

2. *Ocular Lesions*—There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis associated with use of OC's. Discontinue OC's if there is unexplained, sudden or gradual, partial or complete loss of vision; onset of proptosis or diplopia, papilledema, or retinal-vascular lesions, and institute appropriate diagnostic and therapeutic measures.

3. *Carcinoma*—Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases frequency of carcinoma of the breast, cervix, vagina, and liver. Certain synthetic progestogens, none currently contained in OC's, have been noted to increase incidence of mammary nodules, benign and malignant, in dogs. In humans, 3 case-control studies have reported an increased risk of endometrial carcinoma associated with prolonged use of exogenous estrogen in postmenopausal women. One publication reported on the first 21 cases submitted by physicians to a registry of cases of adenocarcinoma of the endometrium in women under 40 on OC's. Of cases found in women without predisposing risk factors (e.g., irregular bleeding at the time OC's were first given, polycystic ovaries), nearly all occurred in women who had used a sequential OC. These are no longer marketed. No evidence has been reported suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only OC's. Several studies have found no increase in breast cancer in women taking OC's or estrogens. One study, however, while also noting no overall increased risk of breast cancer in women on OC's, found an excess risk in subgroups of OC users with documented benign breast disease. Reduced occurrence of benign breast tumors in users of OC's has been well documented. In summary, there is at present no confirmed evidence from human studies of increased risk of cancer associated with OC's. Close clinical surveillance of all women on OC's is, nevertheless, essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer or with breast nodules, fibrocystic disease, or abnormal mammograms should be monitored with particular care if they elect to use OC's.

4. *Hepatic Tumors*—Benign hepatic adenomas have been found to be associated with use of OC's. One study showed that OC's with high hormonal potency were associated with higher risk than lower potency OC's. Although benign, hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage. This has been reported in short-term as well as long-term users. Two studies relate risk with duration of use of OC's, the risk being much greater after 4 or more years' use. While hepatic adenoma is rare, it should be considered in women presenting abdominal pain and tenderness, abdominal mass or shock. A few cases of hepatocellular carcinoma have been reported in women on OC's. Relationship of these drugs to this type of malignancy is not known.

5. *Use in or Immediately Preceding Pregnancy; Birth Defects in Offspring, and Malignancy in Female Offspring*—Use of female sex hormones—both estrogenic and progestational agents—during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, have increased risk of developing in later life a form of vaginal or cervical cancer ordinarily extremely rare. This risk has been estimated to be of the order of 1 in 1,000 exposures or less. Although there is no evidence now that OC's further enhance risk of developing this type of malignancy, such patients should be monitored with particular care if they elect to use OC's. Furthermore, 30 to 90% of such exposed women have been found to have epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether this condition is a precursor of vaginal malignancy. Male children so exposed may develop abnormalities of the urogenital tract. Although similar data are not available with use of other estrogens, it cannot be presumed they would not induce similar changes. An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with use of sex hormones, including OC's, in pregnancy. One case-control study estimated a 4.7-fold increase in risk of limb-reduction defects in infants exposed in utero to sex hormones (OC's, hormonal withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some exposures involved only a few days. Data suggest that risk of limb-reduction defects in exposed fetuses is somewhat less than 1 in 1,000 live births. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective. There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing OC's. Embryos with these anomalies are virtually always aborted spontaneously. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping OC's is unknown. It is recommended that, for any patient who has missed 2 consecutive periods, pregnancy should be ruled out before continuing OC's. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at time of first missed period, and further use of OC's should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus, and advisability of continuation of the pregnancy should be discussed. It is also recommended that women who discontinue OC's with intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive. Many clinicians recommend 3 months, although no precise information is available on which to base this. The administration of progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy.

6. *Gallbladder Disease*—Studies report increased risk of surgically confirmed gallbladder disease in users of OC's and estrogens. In one study, increased risk appeared after 2 years' use and doubled after 4 or 5 years' use. In one of the other studies, increased risk was apparent between 6 and 12 months' use.

7. *Carbohydrate and Lipid Metabolic Effects*—Decrease in glucose tolerance has been observed in a significant percentage of patients on OC's. For this reason, prediabetic and diabetic patients should be carefully observed while on OC's. Increase in triglycerides and total phospholipids has been observed in patients on OC's, clinical significance of this finding remains to be defined.

8. *Elevated Blood Pressure*—Increase in blood pressure has been reported in patients on OC's. In some women, hypertension may occur within a few months of beginning OC's. In the 1st year of use, prevalence of women with hypertension is low in users and may be no higher than that of a comparable group of nonusers. Prevalence in users increases, however, with longer exposure, and in the 5th year of use is 2½ to 3 times the reported prevalence in the 1st year. Age is also strongly correlated with development of hypertension in OC users. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure on OC's. Hypertension that develops as a result of taking OC's usually returns to normal after discontinuing the drug.

9. *Headache*—Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of OC's and evaluation of the cause.

10. *Bleeding Irregularities*—Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing OC's. In breakthrough bleeding, as in all cases of irregular vaginal bleeding, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or change to another OC may solve the problem. Changing to an OC with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary, since this may increase risk of thromboembolic disease. Women with past history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrheic after discontinuing OC's. Women with these pre-existing problems should be advised of this possibility and encouraged to use other methods. Post-use anovulation, possibly prolonged, may also occur in women without previous irregularities.

11. *Ectopic Pregnancy*—Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

12. *Breast-feeding*—OC's given in the postpartum period may interfere with lactation and decrease quantity and quality of breast milk. Furthermore, a small fraction of the hormones in OC's has been identified in the milk of mothers on OC's, effects, if any, on the breast-fed child have not been determined. If feasible, defer OC's until infant has been weaned.

Precautions—GENERAL—1. A complete medical and family history should be taken prior to initiation of OC's. Pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Pap smear and relevant laboratory tests. As a general rule OC's should not be prescribed for longer than 1 year without another physical examination.

2. Under influence of estrogen-progestogen preparations, pre-existing uterine leiomyomata may increase in size.

3. Patients with history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while on OC's should stop OC's and use an alternate method to try to determine whether the symptom is drug-related.

4. OC's may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, asthma, or cardiac or renal insufficiency.

5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence while on OC's. If jaundice develops, OC's should be discontinued.

6. Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution.

7. OC users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency. Clinical significance is undetermined.

8. Serum folate levels may be depressed by OC's. Since the pregnant woman is predisposed to development of folate deficiency and incidence of folate deficiency increases with increasing gestation, it is possible that if a woman becomes pregnant shortly after stopping OC's, she may have a greater chance of developing folate deficiency and complications attributed to this deficiency.

9. The pathologist should be advised of OC therapy when relevant specimens are submitted.

10. Certain endocrine- and liver-function tests and blood components may be affected by estrogen-containing OC's: a. Increased sulfobromophthalein retention. b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. c. Increased thyroid-binding globulin (TBG) leading to increased circulating total-thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered. d. Decreased pregnanediol excretion. e. Reduced response to metyrapone test.

Information for the Patient—See Patient Package Labeling.

Drug Interactions—Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin. A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, ampicillin and tetracycline.

Carcinogenesis—See Warnings on carcinogenic potential of OC's.

Pregnancy—Category X. See Contraindications, Warnings.

Nursing Mothers—See Warnings.

Adverse Reactions—An increased risk of these serious adverse reactions has been associated with use of OC's (see Warnings): thrombophlebitis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, cerebral hemorrhage, hypertension, gallbladder disease, benign hepatomas, congenital anomalies. There is evidence of an association between the following conditions and use of OC's although additional confirmatory studies are needed: mesenteric thrombosis, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions have been reported in patients on OC's and are believed to be drug-related: Nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10 percent or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally: Gastrointestinal symptoms (such as abdominal cramps and bloating); breakthrough bleeding; spotting; change in menstrual flow; dysmenorrhea, amenorrhea during and after treatment; temporary infertility after discontinuance of treatment; edema; chloasma or melasma which may persist; breast changes: tenderness, enlargement, and secretion; change in weight (increase or decrease); change in cervical erosion and cervical secretion; possible diminution in lactation when given immediately postpartum; cholestatic jaundice; migraine; increase in size of uterine leiomyomata; rash (allergic); mental depression; reduced tolerance to carbohydrates; vaginal candidiasis; change in corneal curvature (steepening); intolerance to contact lenses.

The following adverse reactions have been reported in users of OC's, and the association has been neither confirmed nor refuted: premenstrual-like syndrome, cataracts, changes in libido, chorea, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, vaginitis, porphyria.

Acute Overdose—Serious ill effects have not been reported following acute ingestion of large doses of OC's by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

LO/OVRAL® each tablet contains 0.3 mg norgestrel with 0.03 mg ethinyl estradiol.

Wyeth Laboratories Phila., Pa. 19101

CONTINUING MEDICAL EDUCATION

California, Hawaii, Nevada; Alaska, Montana, Idaho; New Mexico; Oregon; Washington; Utah

CALIFORNIA, HAWAII and NEVADA

This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000, ext. 146. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

March 14-21—**9th Obstetric Anesthesia Conference.** Ohio State Univ. at Sheraton Waikiki, Honolulu. One week. 25 hrs. Contact: Excursions Unlimited, Inc., c/o OSU Dept. of Anesthesiology, 1820 Northwest Blvd., Columbus, OH 43212. (800) 848-4438.

April 6-10—**California Society of Anesthesiologists—Hawaiian Seminar.** Kauai Surf Hotel, Kauai. Monday-Friday. 26 hrs. $200, members; $250, nonmembers. Contact: CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

May 3-9—**17th Biennial Western Conference on Anesthesiology.** Hawaiian Regent Hotel, Waikiki (3-7) and Intercontinental Hotel, Maui (8-9). One week. 26 hrs. Contact: Biennial Western Conf. on Anesthesiology, Group Travel Unlimited, 700 Larkspur Landing Circle, Suite 169, Larkspur 94939.

June 4-7—**California Society of Anesthesiologists—Annual Scientific Meeting.** Hyatt Regency, San Francisco. Thursday-Sunday. 20 hrs. $100, members; $200, nonmembers. Contact: CSA, 100 E. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

August 23-25—**Neuro-Anesthesia.** UCSD at Village Inn, La Jolla. Sunday-Tuesday.

September 12-13—**Weekend Seminar.** Calif. Society of Anesthesiologists at Sahara Hotel, Lake Tahoe. Saturday-Sunday. Contact: CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

CANCER

April 25—**Oncology Update: 1981.** Northridge Hospital at Century Plaza Hotel, Los Angeles. Saturday. 8 hrs. $125. Contact: Sandra Rozzen, Dept. of Med. Ed., Northridge Hosp., 18300 Roscoe Blvd., Northridge 91328. (213) 885-3311.

May 18-22—**Medical Oncology Review.** American College of Physicians at University of Hawaii School of Medicine, Honolulu. Monday-Friday. Contact: Postgraduate Dept., ACP, 4200 Pine St., Philadelphia, PA 19104. (215) 243-1200.

June 10—**Carcinomas of the Uterus and Ovaries.** LLU. Wednesday. 4 hrs. $30.

June 13-17—**Head and Neck Oncology.** UCLA. Saturday-Wednesday.

EMERGENCY MEDICINE

March 16-20—**Postgraduate Institute for Emergency Room Physicians, Symposium II.** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $425.

March 27-29—**Emergencies in Clinical Practice: Recognition and Management.** The Cypress Foundation and UCLA at Hyatt Del Monte, Monterey. Friday-Sunday. 14 hrs. Contact: Robert S. Meyer, The Cypress Fndn., P.O. Box 80308, Salinas 93912. (408) 455-1833.

April 18-25—**Emergency Medical Care.** Univ. of Washington School of Medicine at Wailea Beach, Maui. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

April 24-26—**Advanced Cardiac Life Support Workshops.** Emergency Medical Systems at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact. EMS, 2310 Mason St., San Francisco 94133. (415) 956-5900.

April 25-May 2—**Emergency Medicine.** USC at Royal Lahaina Hotel, Maui. One week. $350.

(Continued on Page 21)

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center 2801 Atlantic Ave., Long Beach 90801. (213) 595-3837.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

When she can't manage, you can.

The sweats. The hot flushes. The distress and discomfort of atrophic vaginitis. The possibility of osteoporosis.* The menopause.

For many women, it's a time of confusion and frustration. Counseling can help her overcome these feelings. But counseling *can't* stop vasomotor and vaginal symptoms, or retard bone loss*...the true signs of estrogen deficiency. And that's where she needs you most.

You're an expert at estrogen replacement. You know why it should be used. When it's best avoided. How to cycle therapy. Determine dosage. Check for contraindications and possible complications. Follow-up. You know when therapy should begin, and when it deserves to end.

Most of all, you know your patient—and when she needs the effective relief you can give her with PREMARIN.

When it comes to managing the estrogen-deficiency symptoms of the menopause, you've got what it takes.

*Conjugated Estrogens Tablets have been evaluated as probably effective for postmenopausal osteoporosis

Prescribed with care by physicians who care.

PREMARIN®
BRAND OF
CONJUGATED ESTROGENS TABLETS, U.S.P.
0.3 mg/0.625 mg/1.25 mg/2.5 mg

Please see following page for brief summary of prescribing information

BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION, SEE PACKAGE CIRCULAR)

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA.

Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year[1-3] This risk was independent of the other known risk factors for endometrial cancer These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade[4] The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4 5 to 13 9 times greater than in nonusers The risk appears to depend on both duration of treatment[1] and on estrogen dose[3] In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration,[3] it therefore appears prudent to utilize such a regimen Close clinical surveillance of all women taking estrogens is important In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare[5,6] This risk has been estimated as not greater than 4 per 1000 exposures[7] Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis,[8-12] epithelial changes of the vagina and cervix Although these changes are histologically benign, it is not known whether they are precursors of malignancy Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects[13-16] One case control study[16] estimated a 4 7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion) Some of these exposures were very short and involved only a few days of treatment The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000 In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

DESCRIPTION: PREMARIN (Conjugated Estrogens Tablets, U.S.P.) for oral administration contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications for use as follows.

Effective:

1 Moderate to severe *vasomotor* symptoms associated with the menopause (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions)

2 Atrophic vaginitis

3 Kraurosis vulvae

4 Female hypogonadism

5 Female castration

6 Primary ovarian failure

7 Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease

8 Prostatic carcinoma—palliative therapy of advanced disease

9 Postpartum breast engorgement—Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens[19]

PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING)

"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy and good general health-promoting measures Final classification of this indication requires further investigation

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions 1 Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease 2 Known or suspected estrogen-dependent neoplasia 3 Known or suspected pregnancy (See Boxed Warning) 4 Undiagnosed abnormal genital bleeding 5 Active thrombophlebitis or thromboembolic disorders 6 A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy)

WARNINGS: At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast,[17] although a recent study has raised this possibility.[18] There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens[17]

Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement, it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement[19-22] Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction[23-30] Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users.[31,32] An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives[33,34] If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization Estrogens should not be used in persons with active thrombophlebitis, thromboembolic disorders, or in persons with a history of such disorders in association with estrogen use They should be used with caution in patients with cerebral vascular or coronary artery disease Large doses (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown[35] to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis When doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered

Benign hepatic adenomas should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives[36] Increased blood pressure may occur with use of estrogens in the menopause[37] and blood pressure should be monitored with estrogen use A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives For this reason, diabetic patients should be carefully observed Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases

PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed Conditions influenced by fluid retention such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc Oral contraceptives appear to be associated with an increased incidence of mental depression[21a] Patients with a history of depression should be carefully observed Preexisting uterine leiomyomata may increase in size during estrogen use The pathologist should be advised of estrogen therapy when relevant specimens are submitted If jaundice develops in any patient receiving estrogen therapy, medication should be discontinued while the cause is investigated Estrogens should be used with care in patients with impaired liver function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete

The following changes may be expected with larger doses of estrogen

a Increased sulfobromophthalein retention

b Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability

c Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered

d Impaired glucose tolerance

e Decreased pregnanediol excretion

f Reduced response to metyrapone test

g Reduced serum folate concentration

h Increased serum triglyceride and phospholipid concentration

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhea, premenstrual-like syndrome, amenorrhea during and after treatment, increase in size of uterine fibromyomata, vaginal candidiasis, change in cervical erosion and degree of cervical secretion; cystitis-like syndrome, tenderness, enlargement, secretion from breasts), nausea, vomiting, abdominal cramps, bloating; cholestatic jaundice, chloasma or melasma which may persist when drug is discontinued, erythema multiforme, erythema nodosum, hemorrhagic eruption, loss of scalp hair, hirsutism, steepening of corneal curvature, intolerance to contact lenses, headache, migraine, dizziness, mental depression, chorea, increase or decrease in weight, reduced carbohydrate tolerance, aggravation of porphyria edema, changes in libido

ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females

DOSAGE AND ADMINISTRATION: 1 *Given cyclically for short term use only* For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0 3 to 1 25 mg or more daily)

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible

Administration should be cyclic (*e g* three weeks on and one week off)

Attempts to discontinue or taper medication should be made at three to six month intervals

2 *Given cyclically* Female hypogonadism Female castration Primary ovarian failure Osteoporosis

Female hypogonadism—2 5 to 7 5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration If bleeding does not occur by the end of this period, the same dosage schedule is repeated The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium

If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U S P), 2 5 to 7 5 mg daily in divided doses, for 20 days During the last five days of estrogen therapy, give an oral progestin If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding

Female castration and primary ovarian failure—1 25 mg daily, cyclically Adjust upward or downward according to response of the patient For maintenance, adjust dosage to lowest level that will provide effective control

Osteoporosis (to retard progression)—1 25 mg daily, cyclically

3 *Given for a few days* Prevention of postpartum breast engorgement—3 75 mg every four hours for five doses, or 1 25 mg every four hours for five days

4 *Given chronically* Inoperable progressing prostatic cancer—1 25 to 2 5 mg three times daily

Inoperable progressing breast cancer in appropriately selected men and postmenopausal women—10 mg three times daily for a period of at least three months.

Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding

HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U S P) No 865—Each *purple* tablet contains 2 5 mg in bottles of 100 and 1,000 No 866—Each *yellow* tablet contains 1 25 mg in bottles of 100 and 1,000 Also in unit dose package of 100 No 867—Each *red* tablet contains 0 625 mg in bottles of 100 and 1,000. Also in unit dose package of 100 No 868—Each *green* tablet contains 0 3 mg in bottles of 100 and 1,000

PHYSICIAN REFERENCES: 1 Ziel, H K, *et al* N Engl J Med *293* 1167-1170, 1975 2 Smith, D C, *et al* N Engl J Med *293* 1164-1167, 1975 3 Mack, T M, *et al* N Engl J Med *294* 1262-1267, 1976 4 Weiss, N S, *et al* N Engl J Med *294* 1259-1262, 1976 5 Herbst, A L, *et al* N Engl J Med *284* 878-881, 1971 6 Greenwald, P, *et al* N Engl J Med *285* 390-392, 1971 7 Lanier, A, *et al* Mayo Clin Proc *48* 793-799, 1973 8 Herbst, A, *et al* Obstet Gynecol *40* 287-298, 1972 9 Herbst, A, *et al* Am J Obstet Gynecol *118* 607-615, 1974 10 Herbst, A, *et al* N Engl J Med *292* 334-339, 1975 11 Stafl, A, *et al* Obstet Gynecol *43* 118-128, 1974 12 Sherman, A I, *et al* Obstet Gynecol *44* 531-545, 1974 13 Gal, I, *et al* Nature *216* 83, 1967 14 Levy, E P, *et al* Lancet *1* 611, 1973 15 Nora, J, *et al* Lancet *1* 941-942, 1973 16 Janerich, D T, *et al* N Engl J Med *291* 697-700, 1974 17 Boston Collaborative Drug Surveillance Program N Engl J Med *290* 15-19, 1974 18 Hoover, R, *et al* N Engl J Med *295* 401-405, 1976 19 Daniel, D G, *et al* Lancet *2* 287-289, 1967 20 The Veterans Administration Cooperative Urological Research Group J Urol *98* 516-522, 1967 21 Bailar, J C Lancet *2* 560, 1967 22 Blackard, C, *et al* Cancer *26* 249-256, 1970 23 Royal College of General Practitioners J R Coll Gen Pract *13* 267-279, 1967 23a Royal College of General Practitioners Oral Contraceptives and Health, New York, Pitman Corp, 1974 24 Inman, W H W, *et al* Br Med J *2* 193-199, 1968 25 Vessey, M P, *et al* Br Med J *2* 651-657, 1969 26 Sartwell, P E, *et al* Am J Epidemiol *90* 365-380, 1969 27 Collaborative Group for the Study of Stroke in Young Women N Engl J Med *288* 871-878, 1973 28 Collaborative Group for the Study of Stroke in Young Women JAMA *231* 718-722, 1975 29 Mann, J I, *et al* Br Med J *2* 245-248, 1975 30 Mann, J I, *et al* Br Med J *2* 241-245, 1975 31 Inman, W H W, *et al* Br Med J *2* 203-209, 1970 32 Stolley, P D, *et al* Am J Epidemiol *102* 197-208, 1975 33 Vessey, M P, *et al* Br Med J *3* 123-126, 1970 34 Greene, G R, *et al* Am J Public Health *62* 680-685, 1972 35 Coronary Drug Project Research Group JAMA *214* 1303-1313, 1970 36 Mays, E T, *et al* JAMA *235* 730-732, 1976 37 Pfeffer, R I, *et al* Am J Epidemiol *103* 445-456, 1976

7457/18

Ayerst AYERST LABORATORIES New York, N.Y. 10017

(Continued from Page 17)

April 27-May 1—**Advanced Problems in Cardiac Emergencies.** UCSD at Kauai, Hawaii. Monday-Friday. 21 hrs. $325.

May 4-8—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $425.

May 7-9—**Cardiovascular Emergencies.** See Medicine, May 7-9.

May 13—**Emergency Medicine.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6 hrs. $35. Contact: Cont. Med. Ed., N. T. Enloe Mem. Hosp., 5th Ave. and The Esplanade, Chico 95926. (800) 822-8102, ext. 7375.

May 25-26—**Advanced Cardiac Life Support.** Emergency Care Education Center at Queen Mary, Long Beach. Monday-Tuesday. 12 hrs. $130. Contact: ECEC, P.O. Box 9639, Marina Del Rey 90291. (213) 822-1312.

May 26-30—**California Chapter, American College of Emergency Physicians—10th Annual Scientific Assembly.** Hyatt on Union Square, San Francisco. Tuesday-Saturday. Contact: Calif. Chap., ACEP, 6839 Lincoln Blvd., Suite 240, Los Angeles 90045.

May 28-30—**3rd Annual Trauma Seminar.** DREW at Disneyland Hotel, Anaheim. Thursday-Saturday. Contact: S. Balasubramaniam, MD, Div. of Emergency Medicine, Charles R. Drew Postgraduate Medical School, 1621 E. 120th St., Los Angeles 90059. (213) 603-5235.

June 15-19—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $425.

June 29-July 3—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

July 24-26—**Advanced Cardiac Life Support Workshops.** Emergency Medical Systems at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact. EMS, 2310 Mason St., San Francisco 94133. (415) 956-5900.

July 27-28—**Advanced Cardiac Life Support.** Emergency Care Education Center at Queen Mary, Long Beach. Monday-Tuesday. 12 hrs. $130. Contact: ECEC, P.O. Box 9639, Marina Del Rey 90291. (213) 822-1312.

August 3-7—**Postgraduate Institute for Emergency Room Physicians, Symposium II.** UCSD. Monday-Friday. 40 hrs. $425.

September 14-18—**Postgraduate Institute for Emergency Room Physicians, Symposium I.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $425.

September 28-29—**Advanced Cardiac Life Support.** Emergency Care Education Center at Queen Mary, Long Beach. Monday-Tuesday. 12 hrs. $130. Contact: ECEC, P.O. Box 9639, Marina Del Rey 90291. (213) 822-1312.

MEDICINE

March 15-18—**Symposium on Gastroenterology.** UCSF at Ahwahnee Hotel, Yosemite. Sunday-Wednesday.

March 15-19—**American College of Cardiology.** San Francisco. Sunday-Thursday. Contact: ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

March 23-April 4—**Intensive Review of Internal Medicine—29th Annual.** USC. Two weeks.

March 27-29—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Aladdin Hotel, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

March 29-April 1—**Basic Cardiology for the Practicing Physician.** UCSF at Hyatt, Lake Tahoe. Sunday-Wednesday. 13 hrs. $175.

April 2-3—**Gastroenterology for the Practicing Internist.** UCLA at Palm Springs. Thursday-Friday.

April 4-5—**Infectious Disease for the Practicing Internist.** UCLA at Palm Springs. Saturday-Sunday.

April 5-8—**Cosmetics for the Clinician: A Symposium for Dermatologists.** UCD at Ahwahnee Hotel, Yosemite. Sunday-Wednesday.

April 6-15—**Cardiology for the Consultant: A Clinician's Retreat.** American College of Cardiology at Rancho Santa Fe. 10 days. Contact: Registration Sec., Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

April 8—**Cardiology Symposium.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6 hrs. $35. Contact: Cont. Med. Ed., N. T. Enloe Memorial Hosp., 5th Ave and The Esplanade, Chico 95926. (800) 822-8102, ext. 7375.

April 8—**Annual Physicians' Cardiovascular Symposium.** American Heart Assn., Central Valley Chapter, at Hilton, Fresno. Wednesday. Contact: Genny Berry, AHA, Central Valley Chap., 3835 N. West Ave., Fresno 93705. (209) 224-8215.

April 8—**Apheresis Symposium.** Hospital of the Good Samaritan, Los Angeles. Wednesday. 6 hrs. Contact: Mary Jane Thompson, Hosp. of the Good Samaritan, 616 S. Witmer St., Los Angeles 90017. (213) 977-2345.

April 8-10—**Update in Pediatric Pulmonary and Intensive Care.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. Contact: Prog. Coordinator, Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

April 8-11—**California Blood Bank System—29th Annual Meeting.** Hyatt Airport Hotel, Los Angeles. Wednesday-Saturday. Contact: Mrs. Beverley Hayhurst, Exec. Sec., CBBS, P.O. Box 5401, San Bernardino 92412. (714) 885-6503.

April 10—**22nd Annual Physicians' Symposium: Hearts, Hypertension and Health.** American Heart Assn., Santa Clara County Chap., at LeBaron Hotel, San Jose. Friday. 6 hrs. $35. Contact: Harriet M. Schutte, RN, PhD, AHA, Santa Clara Co. Chap., 3003 Moorpark Ave., San Jose 95128. (408) 247-8555.

April 10-12—**Cardiac Ischemia and Arrhythmias—Current Concepts for Diagnosis and Treatment.** International Medical Education Corp at Sheraton, Anaheim. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

May 1-2—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Sheraton Fisherman's Wharf, San Francisco. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

May 2-3—**Practical Dermatology.** UCLA at Hotel Biltmore, Santa Barbara. Saturday-Sunday.

May 6—**Respiratory.** St. Francis Medical Center, Lynwood. Wednesday. 6 hrs. Contact: Allan M. Hoffman, EdD, Dir. of Med. Ed., St. Francis Med. Ctr., 3630 Imperial Highway, Lynwood 90262. (213) 603-6174.

May 6—**Thyroid '81.** Hospital of the Good Samaritan at Bonaventure Hotel, Los Angeles. Wednesday. 7 hrs. Contact: Mary Jane Thompson, Hosp. of the Good Samaritan, 616 S. Witmer St., Los Angeles 90017. (213) 488-8908.

(Continued on Page 42)

Classified Advertisements

The rate for each insertion is **4.00 per line** (average six words per line) **with five line minimum.**

Box number charge: $2.00 each month.

Classified display rates $40.00 per inch.

Copy for classified advertisements should be received not later than **the fifth of the month preceding issue. All copy must be typed or printed.** • Classified advertisers using Box Numbers forbid the disclosure of their Identity. Your inquiries in writing will be forwarded to Box Number advertisers. The right is reserved to reject or modify all classified advertising copy in conformity with the rules of the Advertising Committee.

Please Type or Print Advertising Copy

CLASSIFIED ADVERTISEMENTS ARE PAYABLE IN ADVANCE

PHYSICIANS WANTED

CALIFORNIA: Faculty member for Family Practice Residency Program located in Orange County. Prefer Residency trained, Board Certified Family Physician. Practice and/or teaching experience preferred. Responsibilities include In-patient coordination of Residency Program or Out-Patient teaching activities. Salary negotiable. Program affiliated with University of Southern California, School of Medicine. Send all inquiries and CV to: J. Blair Pace, MD, Director, Family Practice Residency Program, Santa Ana-Tustin Community Hospital, 1001 North Tustin Avenue, Santa Ana, CA 92705. Phone: (714) 835-3555.

PHYSICIANS WANTED

GROW WITH US IN SUNNY ARIZONA—The INA Healthplan needs physicians in family practice and most specialties in Tucson and Phoenix. Attractive salaries and comprehensive benefits including a professional development program, retirement plan, and group incentive bonus are provided. If team interaction and casual living appeal to you, send your CV to: Professional Relations, INA Healthplan, Inc., 6115 North 7th Street, Phoenix, AZ 85014.

SANTA BARBARA, CALIFORNIA—53 Physician Group Practice has immediate openings in: Family Practice, Nephrology, Obstetrics/Gynecology, Oncology, Orthopedic Surgery, Pulmonary Disease, Urology, to join expanding departments in multi-specialty clinic in operation since 1921. Excellent benefit package. Must have U.S. citizenship, Board certified or eligible. CV to: Administration, Santa Barbara Medical Foundation Clinic, P.O. Box 1200, Santa Barbara, CA 93102.

SAN FRANCISCO. GP, FP, or Internist to join 3 man FG group, must be interested to become partner after 1 year. Adjacent St. Luke's Hospital. For further details call or write, L. D. Duffield, MD, 3620 Army St., San Francisco, CA 94110. Tel: (415) 826-7575.

LARGE SOUTHERN CALIFORNIA Internal Medicine and Medical Subspecialty group is seeking an internist with subspecialty in rheumatology. Contact P.O. Box 22683, San Diego, CA 92122.

EMERGENCY DEPARTMENT OPENING—Permanent and Part-Time in our group. First year salary of $78,000 includes profit sharing and pension plan, educational allowance health insurance, and part time paid at $50 per hour. Malpractice paid. Full time averages less than 40 hours per week. ED sees 43,000 annually in a 300 bed acute care hospital located in Fresno, CA. Near the High Sierras and other recreational areas. Contact Larry Marks, MD, 546 W. Morris, Fresno, CA 93704, or call collect (209) 431-3645.

ORTHOPEDIC SURGERY
OB/GYN
OTOLARYNGOLOGY
GENERAL SURGERY

We have immediate need of physicians in these and other disciplines to join us at INA/Ross-Loos Healthplan, now marking a half-century of service to Southern California members.

INA/Ross-Loos health centers are located throughout the region providing comprehensive care through utilization of community hospitals.

We offer the board eligible/certified physician an opportunity to grow with us in an environment of challenge, freedom from malpractice premiums, minimized paperwork and excellent fringe benefits.

Our compensation is highly competitive. Request details by phone or letter to:

ROSS LOOS MEDICAL GROUP INC

ALLAN S. MIRKEN, MD
Director of Medical Personnel
INA/Ross-Loos Medical Center
1711 West Temple Street
Los Angeles, CA 90026
(213) 413-1313

PHYSICIANS WANTED

INTERNIST/GI to join a 13-physician, multispecialty group in Mount Vernon, Washington. The Medical Center is located across the street from a 126-bed hospital. Stockholder status is possible after one year. Guaranteed first year salary plus liberal fringe benefits. Position available June, 1981. Contact Shane Spray, Administrator, Skagit Valley Medical Center, 1400 Kincaid, Mount Vernon, WA 98273. (206) 428-2524.

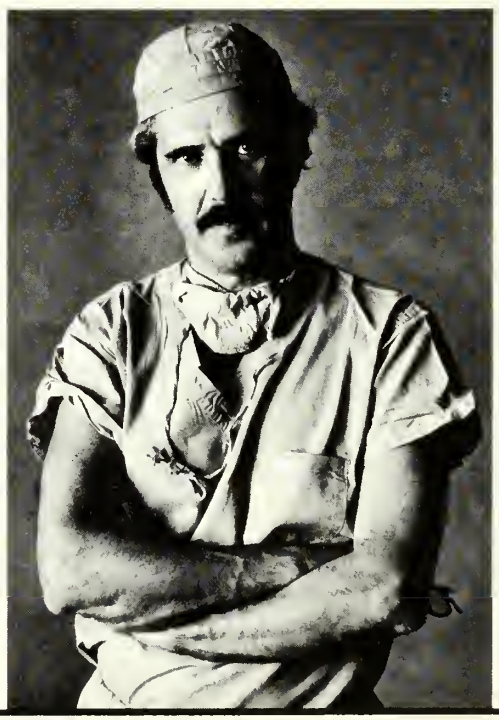
(Continued on Page 24)

We've taken the pain out of establishing your practice.

As a physician you're familiar with ways to alleviate pain. But chances are, your extensive educational process has not prepared you to handle the problems of selecting a location and establishing a successful private practice. National Medical Enterprises' Professional Relations Department has a staff of highly trained people who can help take the anguish out of making this important decision.

If you are familiar with NME you know us as one of America's largest and fastest growing health care companies that owns, operates, and manages acute care facilities that meet or exceed JCAH standards.

NME can provide Board Eligible/Board Certified physicians with private practice opportunities from Seattle, Washington to St. Petersburg, Florida - opportunities that enable you to concentrate on medicine while we assist you through the start-up phase of your new practice.



NME can offer you some of the best equipped health care facilities in the nation along with modern offices, a diverse choice of climates and a community ideally suited to your lifestyle.

Let us take the pain out of establishing a practice for you. Write and send us your curriculum vitae. Let us know your interests and where you want to live and practice. For additional information, contact:

Raymond C. Pruitt
Director, Physician Relations
National Medical Enterprises
11620 Wilshire Blvd.
Los Angeles, California 90025
(213) 479-5526
1-800-421-7470

NME NATIONAL MEDICAL ENTERPRISES, INC.

"The total health care company."

Acute pain is no laughing matter.

The first prescription for the first days of acute pain

Empirin® c̄ Codeine #3

Each tablet contains: aspirin, 325 mg; plus codeine phosphate, 30 mg, (Warning — may be habit-forming). Ⓒ III

For the millions of patients who need the potency of aspirin and codeine for their acute pain.

The pain of fractures, strains, sprains, burns and wounds is at its peak during the first three to four days following trauma. The potent action of Empirin c̄ Codeine begins to work within 15 minutes of oral administration, an important advantage during this acute pain period. Empirin c̄ Codeine has unique bi-level action to attack pain at two critical points: peripherally at the site of injury and centrally at the site of pain awareness.

For the most effective dosage in treating acute pain, begin with...two tablets of Empirin c̄ Codeine #2 or #3, every four hours. Titrate downward as pain subsides.

EMPIRIN® with Codeine

Ⓒ III

DESCRIPTION: Each tablet contains aspirin (acetylsalicylic acid) 325 mg plus codeine phosphate in one of the following strengths: No. 2 — 15 mg, No. 3 — 30 mg, and No. 4 — 60 mg. (Warning — may be habit-forming.)

CONTRAINDICATIONS: Hypersensitivity to aspirin or codeine.

WARNINGS:

Drug dependence: Empirin with Codeine can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of this drug and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral, narcotic-containing medications. Like other narcotic-containing medications, the drug is subject to the Federal Controlled Substances Act.

Use in ambulatory patients: Empirin with Codeine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using this drug should be cautioned accordingly.

Interaction with other central nervous system (CNS) depressants: Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics, or other CNS depressants (including alcohol) concomitantly with Empirin with Codeine may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Use in pregnancy: Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, Empirin with Codeine should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

PRECAUTIONS:

Head injury and increased intracranial pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions: The administration of Empirin with Codeine or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Allergic: Precautions should be taken in administering salicylates to persons with known allergies; patients with nasal polyps are more likely to be hypersensitive to aspirin.

Special risk patients: Empirin with Codeine should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture, peptic ulcer, or coagulation disorders.

ADVERSE REACTIONS: The most frequently observed adverse reactions to codeine include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients and some of these adverse reactions may be alleviated if the patient lies down. Other adverse reactions include euphoria, dysphoria, constipation, and pruritus.

The most frequently observed reactions to aspirin include headache, vertigo, ringing in the ears, mental confusion, drowsiness, sweating, thirst, nausea, and vomiting. Occasional patients experience gastric irritation and bleeding with aspirin. Some patients are unable to take salicylates without developing nausea and vomiting. Hypersensitivity may be manifested by a skin rash or even an anaphylactic reaction. With these exceptions, most of the side effects occur after repeated administration of large doses.

DOSAGE AND ADMINISTRATION: Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. Empirin with Codeine is given orally. The usual adult dose for Empirin with Codeine No. 2 and No. 3 is one or two tablets every four hours as required. The usual adult dose for Empirin with Codeine No. 4 is one tablet every four hours as required.

DRUG INTERACTIONS: The CNS depressant effects of Empirin with Codeine may be additive with that of other CNS depressants. See WARNINGS.

Wellcome

Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

(Continued from Page 22)

PHYSICIANS WANTED

WYOMING: Emergency Medicine—Summer locum tenens for experienced emergency physicians in busy resort hospital located in Jackson, Wyoming. Average of 56 hours per week with flexible scheduling arrangement. Must be available June 5 through September 14 inclusive, without exception. Excellent hourly compensation plus paid professional liability insurance. For further information, contact William Salmo at 1-(800)-525-3681 (in Colorado call collect (303) 471-4981).

ORTHOPEDIC SURGEON—Board Certified, Orthopedic Surgeon needed at VA Medical Center, Livermore, CA. Ideal living, good climate and clean air. Malpractice insurance not needed. Position available at present. Salary dependent upon experience and qualifications. Contact: John F. Kane, MD, Chief of Staff, VA Medical Center, Livermore, CA 94550. Tel: (415) 447-2560, ext. 204.

WANTED: Univ. trained general surgeon needed to join two other general surgeons in 13 man clinic. Excellent qualifications required. Location: southern Idaho, near excellent outdoor recreation. Write Box 1233, Twin Falls, ID 83301

SAN FRANCISCO BAY AREA—45-MD multispecialty private group practice established 25 years ago, seeking an orthopedic surgeon for medical/industrial office work to assist our busy 2 physician department in their general orthopedic work. Excellent location in the Santa Clara Valley, 45 minutes from San Francisco, 10 minutes from Stanford University. Send CV to: Walter Saphir, MD, Sunnyvale Medical Clinic, 596 Carroll St., Sunnyvale, CA 94086.

EMERGENCY MEDICINE OPPORTUNITIES, full and part-time, in the Rocky Mountain states for career oriented emergency physicians. Excellent compensation and paid professional liability insurance. Send credentials to Mr. William Salmo, Chase Stone Center, Holly Sugar Building, Suite 440, Colorado Springs, CO 80903. Or call toll-free 1 (800) 525-3681 (in Colorado call collect (303) 471-4981).

CALIFORNIA, San Jose: Primary Care Physician with experience in Peds. and minor trauma wanted to staff ambulatory care clinic at large teaching hospital in San Francisco Bay Area. Flexible hours, independent contractor status with hourly compensation. For further details, please call or write: Eve Campbell, 1550 The Alameda, No. 314, San Jose, CA 95126. Tele: (408) 293-8881.

ASSISTANT DIRECTOR
Human Services Agency
Mental Health Services

The Orange County Human Services Agency is seeking a highly qualified Mental Health professional to serve as Assistant Agency Director. Responsible for centralized mental health functions and for quality control of mental health services provided within the agency's multi-discipline regional structures. Experienced Psychiatrists, clinical social workers, clinical Psychologists or hospital/health care administrators with strong mental health and administrative background may qualify. Annual salary of $46,200 to $69,720 based on merit. The starting salary is negotiable. Final filing date March 31, 1981.

To apply, contact
HSA, PERSONNEL
515 N. SYCAMORE
SANTA ANA, CALIFORNIA
or call (714) 834-7828

Affirmative Action Employer M/F

PHYSICIANS WANTED

GENERAL SURGEON—needed in established multispecialty clinic in beautiful university town. First year guaranteed with full fringe benefits and incentive, new hospital, four season recreation, and ideal family environment. Contact The Budge Clinic, 225 E. 4th North, Logan, UT 84321.

GENERAL/FAMILY PRACTICE PHYSICIANS (2) needed by 31 member multi-specialty group. Excellent practice opportunity; benefits and retirement program; all practice costs paid; early shareholder status. Reply D. R. Molesworth, Administrator, San Luis Medical Clinic, Ltd., 1235 Osos Street, San Luis Obispo, CA 93401.

CALIFORNIA—B.E./B.C. Family Physician, Emergency Physician or Internist wanted for new multi-Specialty group in desirable Roseville suburb of Sacramento. Combines office practice with part-time Minor Emergency Clinic practice. Competitive salary. Fringe; leads to partnership. Excellent hospital and office facilities. One position avail. immed., one avail. in Spring, 1981. Contact: Joseph Rosenfield, Adm., Western Medical Group, 6330 Main Ave., Orangevale, CA 95662, (916) 988-9544.

INFECTIOUS DISEASE Specialist wanted to join another busy ID Specialist in private practice in growing city in Northwest. Please send CV to Box 6163, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

RADIOLOGIST: Board certified, experienced all major modalities plus board eligible and/or certified in nuclear medicine or equivalent, join group in hospital practice Southern California. Full curriculum vitae initial reply, Box 6177, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

OPHTHALMOLOGIST needed to fill recent vacancy in busy practice designed for 2 physicians. Join Board Certified Ophthalmologist in practice in this friendly Ohio city. General ophthalmology or retina practice. $75,000 plus fringes first year. Full partnership buy in possible after first year. Respond with CV to Box 6183, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

GENERAL PRACTITIONER/F.P.—private practice opportunity in association with acute-care general hospital in Santa Maria, CA. Fully accredited CMA and JCAH with 24-hour E.R. Excellent guarantee of annual gross billings, free office rent, other financial assistance available. Located within 10 miles of beaches and lakes. Interested physicians please send C.V. to Marsha Mayer, Director of Physician Recruiting, SUMMIT HEALTH LTD., 4070 Laurel Canyon Blvd., Studio City, CA 91604, or call collect (213) 985-8386.

POSITIONS AVAILABLE IN GENERAL MEDICINE: Board certified or Board eligible preferred. Beginning salary from $38,000 to $50,000 per year depending upon qualifications, plus automatic pay bonus of $15,000 to $24,500 per year. Complete malpractice insurance coverage provided. Liberal fringe benefits—life insurance, health insurance, retirement, 30 days vacation plus 15 days sick leave each year. An unexcelled opportunity to engage in a challenging medical practice in a rural setting offering unlimited recreational opportunities—hunting, fishing, skiing, plus fresh, clear air in abundance. Contact: Norman C. Jorgenson, MD, Chief of Staff, Veterans Administration Medical Center, Miles City, MT 59301. Telephone (406) 232-3060, or FTS 585-9201. An Equal Opportunity Employer.

CARDIOLOGIST, PULMONOLOGIST, UROLOGIST, DERMATOLOGIST, & ORTHOPEDIC HAND SURGEON: Immediate openings for fully trained, Board Certified or eligible physicians in a multi-specialty group. Complete pulmonary laboratory facilities. Attractive San Francisco Bay Area. Send CV to Recruitment Committee, San Jose Medical Clinic, 45 South 17th Street, San Jose, CA 95112.

Excellent opportunities exist in prime geographical locations throughout the Western, Midwestern and Rocky Mountain states for General and Family Practice Physicians. Access to hunting, fishing, skiing, boating and other excellent recreational activities. Top school systems and warm community atmosphere. Unlimited opportunity to make an impact. Compensation package includes base guarantee, incentives and fringe benefits. Complete medical practice support. The future holds unlimited growth potential. For information contact:

Advanced Health Systems, Inc.
Professional Placement
17861 Cartwright Road
Irvine, CA 92714
or call toll-free (800) 854-3020
EOE M/F

PHYSICIANS WANTED

COLORADO EMERGENCY MEDICINE: Directorship and Clinical positions available in Northeastern portion of the state in moderate volume emergency department. Hourly guarantee plus compensation for Director's added responsibilities. Paid professional liability insurance and other amenities. For further information contact William Salmo toll-free 1 (800) 525-3681 (within Colorado call collect (303) 471-4981); or send credentials in confidence to Chase Stone Center, Holly Sugar Building, Suite 1070, Colorado Springs, CO 80903.

LAS VEGAS, NEVADA: Emergency Medicine Opportunity-Clinical position available in this modern facility south of Las Vegas. Flexible scheduling according to individual needs allows time to enjoy the numerous recreational facilities in the surrounding countryside. Minimum guarantee plus paid professional liability insurance. For details send credentials in confidence to William Salmo, Chase Stone Center, Holly Sugar Building, Suite 1070, Colorado Springs, CO 80903 or call toll-free 1 (800) 525-3681 (within Colorado, call collect (303) 471-4981).

(Continued on Page 34)

DEVELOPMENTAL DISABILITIES PROGRAMS

Opportunities are available for internists, family practitioners and psychiatrists to work with developmentally disabled people in State residential communities. Locations from Los Angeles to northern California. Challenging and varied cases, congenial professional environment, excellent civil service benefits.

Hospital Recruitment Program
Dept. of Developmental Services
714 P Street
Sacramento, CA 95814
(916) 322-1221 collect

DOCTORS' SPECIAL!

Give your family a

Condo Vacation in Hawaii

and we'll give you use of a

Car FREE!

When you stay in a 1-bedroom oceanview or 2-bedroom condominium in one of these luxurious resorts, you'll have the use of a car free. All condominiums are on or near the beach and have daily maid service.

WAIKIKI
Island Colony or Waikiki Sunset
Pool, golf nearby and many luxury extras. From $59/day-$370/week
1-4 persons

MAUI
Kaanapali Shores
Free tennis, pool, golf nearby. From $78/day-$490/week
1-4 persons

HAWAII
Kona Lagoon
Free tennis, golf nearby. From $85/day-$535/week
1-4 persons

KAUAI
Pono Kai
Mile-long beach, free tennis, barbecue area, sauna. From $58/day-$365/week
1-4 persons

Serving Hawaii Visitors for More Than 30 Years

HCP Condo Resorts

Andre S. Tatibouet, President
2299 Kuhio Avenue, Honolulu, Hawaii 96815

For reservations, beautiful four-color brochures or information about any of HCP's 18 hotels and condominiums in Hawaii, see your travel agent or call Hawaii Toll Free 800-367-5124.

Call Hawaii Toll Free 800-367-5124

Environmental Medicine Department Manager

$25,104-$33,276/yearly

The University of California, Irvine is seeking a qualified individual to assume the position of the Manager of the Department of Community and Environmental Medicine.

Under the direction of the department chair, the manager will be responsible for program development and administrative responsibilities in the area of finance, equipment and space, evaluation, and technical and support staff management.

The qualified applicant will have advanced administrative and analytical skills which preferably have been successfully applied in procurement and management of environmental biomedical research grants.

The University of California, Irvine offers excellent benefits including a comprehensive insurance package, ideal location and three weeks paid vacation.

Filing deadline: until filled. Request required application materials for Job #CP 101.

University of California, Irvine
Campus Personnel
152 Administration Bldg.
Irvine, CA 92717

Affirmative Action Employer

UCI

$25,000,000 LOAN FUND

Available to Physicians

Up to $20,000 Entirely by Mail!

Emphatically private. All transactions through plain, unmarked mail. Use the money for anything. We don't ask.

Attractive rates. Turn-around a few short days.

Call **Ron Malcomb** or send coupon for short-form package. It's brief and easy!

THE BANKERS INVESTMENT COMPANY
(213) 577-3049

99 SOUTH LAKE, SUITE 260
LOCK DRAWER JM-1 • P.O. BOX 4602
PASADENA, CALIFORNIA 91101

MR. R. J. MALCOMB, BANKERS INVESTMENT CO
LOCK DRAWER JM-1, P.O. BOX 4602
PASADENA, CALIFORNIA 91101

AMOUNT I WANT $ _____

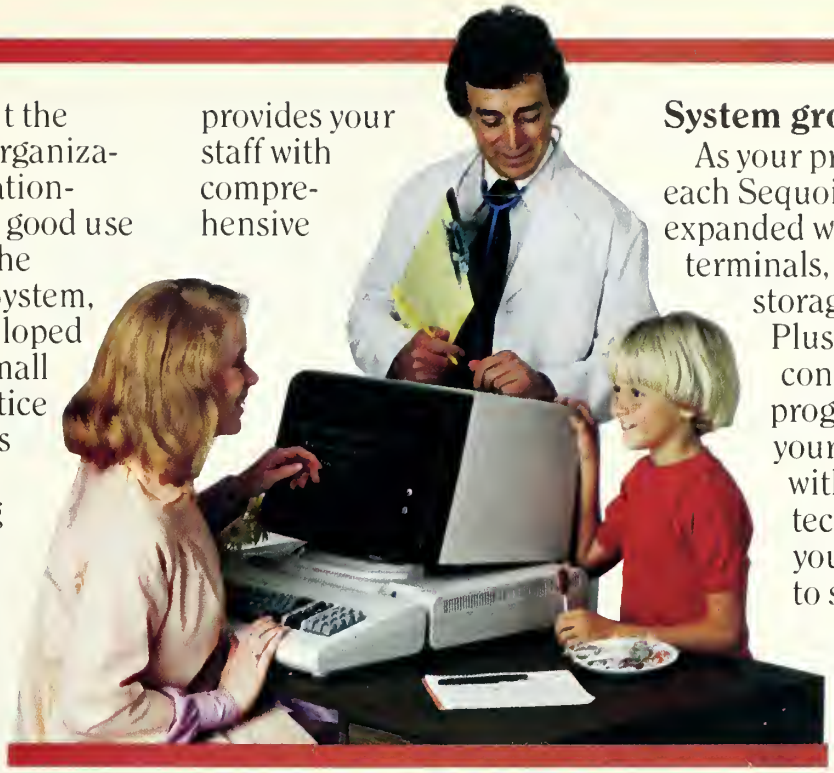
NAME _____

ADDRESS _____

CITY _____ STATE _____

ZIP _____ PHONE _____

The Sequoia Medical Syste
Avoids Complications



The Sequoia Medical System. A sophisticated, efficient office organizer and medical assistant. Designed to be easy to use.

Now you can put the computer's organizational and information-handling power to good use in your practice. The Sequoia Medical System, designed and developed precisely for the small group or solo practice physician, provides complete office support, including financial analysis, third party billing, and patient data management. But most importantly, Sequoia is easy to use.

Ordinary English

No computer knowledge is needed to talk to the Sequoia System. Everything is done in English so plain that you'll forget you're talking to a computer. Sequoia gives you simple instructions, clear task descriptions, and frequent directions along the way. Details on taking the system through its paces are listed—menu style—and displayed in soft, green letters on a swivel screen designed to prevent glare and eye-strain. The keyboard on your terminal will probably look familiar: it's the IBM Selectric now being used in most offices.

Training and support

Prior to installing your medical system, Sequoia provides your staff with comprehensive training at a Sequoia Training Center. After training is completed, you and your staff can use the Sequoia Hot Line to answer any questions that might arise. This Hot Line support even allows us to communicate with your system by telephone from the Sequoia home office.

For further assistance, we also have Customer Support Representatives in local offices throughout the U.S. They're available to visit your office and work with you and your staff on an ongoing basis.

Comprehensive training and continuous support help to make the Sequoia System easy to use.

System growth

As your practice grows, each Sequoia System can be expanded with additional terminals, patient data storage, and programs. Plus, Sequoia continually updates programs to keep your system in step with the latest technology. So you can choose to start with the simplest, least expensive system, and add capabilities as your needs grow. With Sequoia, system growth is flexible and easy.

Specialization

Sequoia was designed specifically for medical practice management. It blends into your office routine with the efficiency of a professional—quickly and easily.

To find out more about Sequoia, write for a free informational brochure to the Sequoia Group, 1100 Larkspur Landing Circle, Larkspur, California 94939. Or dial the toll-free number below and discuss your needs with us. Like our medical system, we're easy to talk to.

Call toll-free **(800) 227-2360**; in California, call **(800) 772-2655.**

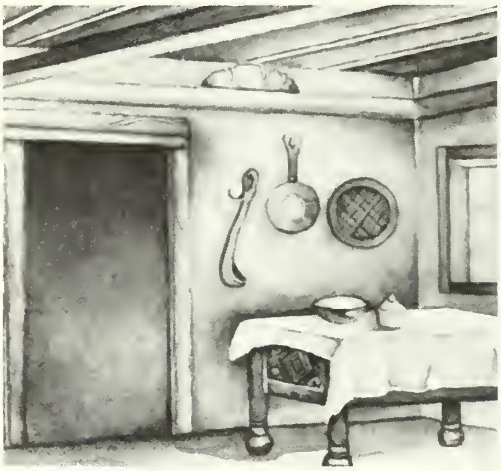
SEQUOIA GROUP™
INCORPORATED

Atlanta, Birmingham, Boston, Buffalo, Charlotte, Chicago, Columbus, Dallas, Denver, Detroit, Hartford, Houston, Indianapolis, Irvine, Kansas City, Los Angeles, Memphis, Miami, Minneapolis, Nashville New Orleans, New York City, Norfolk, Oklahoma City, Philadelphia, Phoenix, Pittsburgh, Portland, Salt Lake City, San Antonio, San Diego, San Francisco, Seattle, St. Louis, Tampa, Washington, D.C.

Visit us in Booths 61 through 66 at the CMA Convention

Yesterday's Folk Remedy:

A rye loaf in the rafters.



Early in this century in Central Europe, almost every farm family kept a loaf of moldy rye bread on one of the kitchen beams. When any family member was cut or bruised, it was an old custom to cut a thin slice from the outside of the loaf, mix it into a paste with water, and apply it to the wound with a bandage. It was believed that no infection would then result from the cut.[1]

Today's Tradition:

Tegopen®

(cloxacillin sodium)

for the treatment* of known or suspected staphylococcal infections such as:

- Acute sinusitis
- Furunculosis and carbuncles
- Impetigo
- Secondarily infected dermatitis
- Cellulitis
- Abscesses
- Infected sebaceous cysts

In serious, deep-seated staph infections, 500 mg q.i.d. dosage is recommended.†

- Tegopen has been reported active against 96% of *Staphylococcus aureus*.[2]
- 80% of *S aureus* has been reported resistant to amoxicillin and ampicillin.‡[2]
- 88% of *S aureus* has been reported resistant to penicillins G and V.‡[2]
- Staph resistance to erythromycin may develop during a course of therapy.[3]

Available as 500-mg and 250-mg capsules and Oral Solution 125 mg/5 ml.

Tegopen® (cloxacillin sodium)
Today's Penicillin for Today's Physician

1. Florey HW, Chain E, Heatley NG, et al: *Antibiotics*. London, Oxford University Press, 1949, p 2
2. Bac-Data Bacteriologic Report, Professional Market Research, 1978-1979. The clinical significance of *in vitro* data is unknown.
3. Erythromycin prescribing information (in *Physicians' Desk Reference*, ed 34. Oradell, NJ, Medical Economics Co, 1980) states that staph resistance may develop during treatment.

See brief summary of prescribing information on an adjoining page.

Copyright © 1981, Bristol Laboratories

*Note: The choice of Tegopen should take into consideration the fact that it has been shown to be effective only in the treatment of infections caused by pneumococci, Group A beta-hemolytic streptococci, and penicillin G-resistant and penicillin G-sensitive staphylococci. If the bacteriology report later indicates that the infection is due to an organism other than a penicillin G-resistant staphylococcus sensitive to cloxacillin sodium, the physician is advised to continue therapy with a drug other than cloxacillin sodium or any other penicillinase-resistant semisynthetic penicillin.

†In serious, life-threatening infections, oral preparations of the penicillinase-resistant penicillins should not be relied on for initial therapy.

‡Not all isolates may have been tested using both discs.

Tegopen®
(cloxacillin sodium)
Capsules and Oral Solution

Brief Summary of Prescribing Information

For complete information, consult Official Package Circular (12) 9/11/75

INDICATIONS

Although the principal indication for cloxacillin sodium is in the treatment of infections due to penicillinase-producing staphylococci, it may be used to initiate therapy in such patients in whom a staphylococcal infection is suspected. (See Important Note below.)

Bacteriologic studies to determine the causative organisms and their sensitivity to cloxacillin sodium should be performed.

IMPORTANT NOTE

When it is judged necessary that treatment be initiated before definitive culture and sensitivity results are known, the choice of cloxacillin sodium should take into consideration the fact that it has been shown to be effective only in the treatment of infections caused by pneumococci, Group A beta-hemolytic streptococci, and penicillin G-resistant and penicillin G-sensitive staphylococci. If the bacteriology report later indicates the infection is due to an organism other than a penicillin G-resistant staphylococcus sensitive to cloxacillin sodium, the physician is advised to continue therapy with a drug other than cloxacillin sodium or any other penicillinase-resistant semi-synthetic penicillin.

Recent studies have reported that the percentage of staphylococcal isolates resistant to penicillin G outside the hospital is increasing, approximating the high percentage of resistant staphylococcal isolates found in the hospital. For this reason, it is recommended that a penicillinase-resistant penicillin be used as initial therapy for any suspected staphylococcal infection until culture and sensitivity results are known.

Cloxacillin sodium is a compound that acts through a mechanism similar to that of methicillin against penicillin G-resistant staphylococci. Strains of staphylococci resistant to methicillin have existed in nature and it is known that the number of these strains reported has been increasing. Such strains of staphylococci have been capable of producing serious disease, in some instances resulting in fatality. Because of this, there is concern that widespread use of the penicillinase-resistant penicillins may result in the appearance of an increasing number of staphylococcal strains which are resistant to these penicillins.

Methicillin-resistant strains are almost always resistant to all other penicillinase-resistant penicillins (cross-resistance with cephalosporin derivatives also occurs frequently). Resistance to any penicillinase-resistant penicillin should be interpreted as evidence of clinical resistance to all, in spite of the fact that minor variations in *in vitro* sensitivity may be encountered when more than one penicillinase-resistant penicillin is tested against the same strain of staphylococcus.

CONTRAINDICATIONS

A history of a previous hypersensitivity reaction to any of the penicillins is a contraindication.

WARNING:

Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents, e.g., pressor amines, antihistamines, and corticosteroids.

Safety for use in pregnancy has not been established.

PRECAUTIONS:

The possibility of the occurrence of superinfections with mycotic organisms or other pathogens should be kept in mind when using this compound, as with other antibiotics. If superinfection occurs during therapy, appropriate measures should be taken.

As with any potent drug, periodic assessment of organ system function, including renal, hepatic, and hematopoietic, should be made during long-term therapy.

ADVERSE REACTIONS:

Gastrointestinal disturbances, such as nausea, epigastric discomfort, flatulence, and loose stools, have been noted by some patients. Mildly elevated SGOT levels (less than 100 units) have been reported in a few patients for whom pretherapeutic determinations were not made. Skin rashes and allergic symptoms, including wheezing and sneezing, have occasionally been encountered. Eosinophilia, with or without overt allergic manifestations, has been noted in some patients during therapy.

USUAL DOSAGE

Adults: 250 mg. q 6h.

Children: 50 mg./Kg./day in equally divided doses q 6h. Children weighing more than 20 Kg. should be given the adult dose. Administer on empty stomach for maximum absorption.

N.B. INFECTIONS CAUSED BY GROUP A BETA-HEMOLYTIC STREPTOCOCCI SHOULD BE TREATED FOR AT LEAST 10 DAYS TO HELP PREVENT THE OCCURRENCE OF ACUTE RHEUMATIC FEVER OR ACUTE GLOMERULONEPHRITIS.

SUPPLIED

Capsules—250 mg. in bottles of 100, 500 mg. in bottles of 100.
Oral Solution—125 mg./5 ml. in 100 ml. and 200 ml. bottles.

BRISTOL®
Bristol Laboratories
Division of Bristol-Myers Company
Syracuse, New York 13201

Summer Cruise/Conferences on Legal-Medical Issues

Approved For 23 CME Credits Category I Towards AMA Physician's Recognition Award.

By the American College of Legal Medicine
Seminars Directed by Irwin N. Perr, M.D., J.D.
Professor, Rutgers Medical School

Caribbean Conference – July 29 – August 8, 1981 aboard TSS Fairwind.* Visit St. Maarten, Antigua, Barbados, Martinique and St. Thomas.

Mediterranean Conference – August 22 – September 5, 1981 aboard Mts. Danae.** Visit major cities in Italy, Greece, Egypt, Israel, Turkey, Yugoslavia.

- **All meals on cruise and aloft.**
- **Seminars conducted at sea.**
- **Alitalia scheduled flights to Italy.**
- **Excellent Fly/Cruise group rates.**
- **Hotel Danieli – Venice, Italy**
- **All transfers**

The number of participants in each Conference is limited. Early registration is advised.

For color brochure and additional information contact:

International Conferences
189 Lodge Avenue
Huntington Station, N.Y. 11746
Phone (516) 549-0869

Both conferences are designed to conform with the 1976 Tax Reform Act.

*Liberian Registry
**Greek Registry

AMERICAN HOLISTIC MEDICAL INSTITUTE
8th Scientic Meeting
HOLISTIC HEALTH:
THE FAMILY PRACTICE OF THE 80's
UNIVERSITY OF WISCONSIN-LA CROSSE
MAY 22 — 28, 1981

Over 60 Workshops and Lectures. Choose a track of general Holism or concentrate in one field: Nutrition, Physical Exercise, Neuromuscular Integration, Osteopathic Manipulative Treatment, Spiritual Attunement, Environmental Medicine, Clinical Ecology, Biomolecular Medicine, Holistic Psychology, Self-regulation, Biofeedback, Holistic Nursing, Holistic Dentistry.

Distinguished Faculty of over 50 Presenters including:

- Tom Ferguson
- Sr. Mary Gregory Hanson
- Jean Houston
- Paul Kimberly
- Suzanne Kobasa
- Irvin Korr
- John Olwin
- Kenneth Pelletier
- Theron Randolph
- Albert Schatz
- Bernard Siegel
- Patricia Sun

As an organization accredited by the Liaison Committee on continuing medical education to provide continuing medical education, the American Holistic Medical Association certifies that this continuing medical offering meets the criteria for 40 hours of LCCME Category I credits provided it is used and completed as designed.

For brochure and registration information:

A H M I
% Division of University Outreach, UW-La Crosse
La Crosse, WI 54601

CLASSIFIED

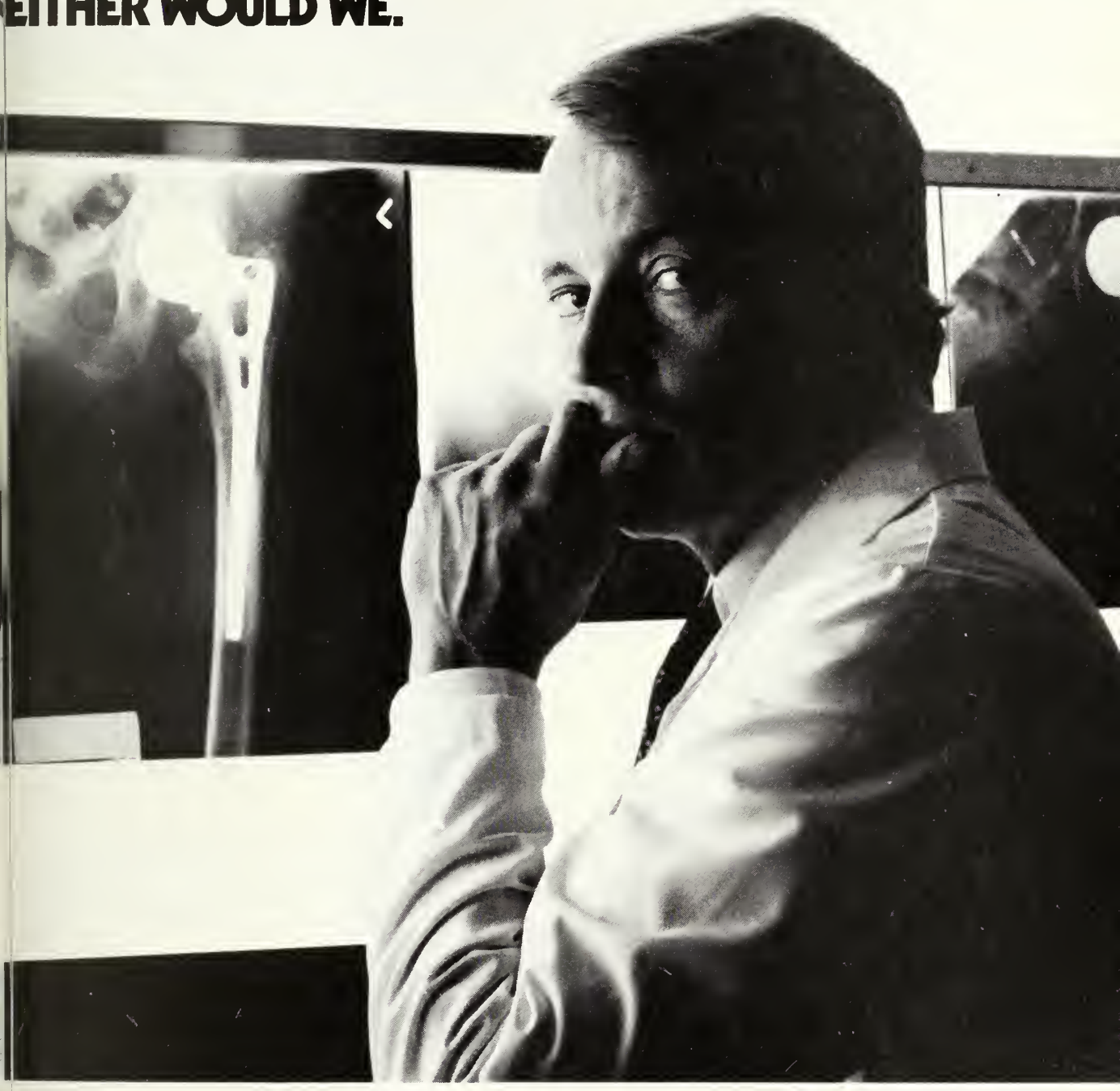
INFORMATION

(415) 777-2000

EX 220

OULD YOU GUARANTEE THERE WON'T BE PROBLEMS VER THE NEXT 5 YEARS?

EITHER WOULD WE.



Responsible physicians know hat despite sound medical judgnent and specialized skills, their prognoses are often subject to ncertainty.

You must make allowances for otential adversity and you should xpect your professional liability nsurance company to do the same.

Responsible medical malpractice nsurers, like The Doctors' Company, now that their policyholders' longange interests are best protected y financial strength and solvency.

That's why we maintain the largest surplus of all the doctor-owned malpractice insurers in the western United States. That's why our earned premium to surplus ratio is the most favorable of all these companies. And that's why we continue to collect surplus contributions from new members.

Future results can't be guaranteed, in the fragile art of medicine or in the volatile business of malpractice insurance. Our allowance for adversity is surplus.

For details about our program, call or write: The Doctors' Company, 233 Wilshire Blvd., Santa Monica, CA 90401. (213) 451-9936. Toll free, (800) 352-7271. Outside California, (800) 421-2368.

THE DOCTORS' COMPANY

AN INTERINSURANCE EXCHANGE
OFFERING MEDICAL MALPRACTICE INSURANCE
TO DOCTORS IN
CALIFORNIA, NEVADA, WYOMING AND MONTANA

In Hypertension*...When You Need to Conserve K^+

Every Step of the Way

Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

†Step 1 usually consists of an initial phase (a diuretic alone), a titration phase (dosage adjustment and/or addition of a K^+ supplement or K^+-sparing agent) and maintenance phase (a diuretic alone or in combination with a K^+ supplement or K^+-sparing agent).

Serum K^+ and BUN should be checked periodically (see Warnings).

Before prescribing, see complete prescribing information in SK&F Co. literature or *PDR*. A brief summary follows:

* **WARNING**
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K^+ frequently, both can cause K^+ retention and elevated serum K^+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded; in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia, although uncommon, has been reported. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth, anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components.

Supplied: Bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

© SK&F Co., 1980

SK&F CO.
a SmithKline company
Carolina, P.R. 00630

THE WESTERN
Journal of Medicine

Refer to: Brasher C, Siegler RL: The hemolytic-uremic syndrome. West J Med 134:193-197, Mar 1981

The Hemolytic-Uremic Syndrome

CRAIG BRASHER, MD, *and* RICHARD L. SIEGLER, MD, *Salt Lake City*

Our experience with 61 episodes of the hemolytic-uremic syndrome in 60 patients showed a mean patient age of 3 years and a higher incidence of the disease during the summer months. Diarrhea, often bloody, preceded the other features of the illness in 93 percent of the cases. Hemolytic anemia, hematuria and proteinuria occurred in all of the patients. Thrombocytopenia and severe azotemia (blood urea nitrogen greater than 100 mg per dl) occurred in 74 percent and 72 percent of the children, respectively. Blood transfusions were necessary in 64 percent and dialysis was required in 54 percent of the cases. Mortality was low (5 percent) and 85 percent of the children had a complete recovery.

THE HEMOLYTIC-UREMIC SYNDROME (HUS) is the most frequent cause of acute renal failure in infants and young children. Its features, which include microangiopathic hemolytic anemia, thrombocytopenia and acute nephropathy, have been described extensively in recent series and reviews.[1-5] While the pathogenesis remains uncertain, a variety of infectious agents may damage the renal vascular endothelium and initiate the coagulation cascade. This in turn traps platelets in the kidney, causes mechanical fragmentation of the erythrocytes and produces acute renal failure.

This report describes our experience with 61 episodes of HUS in 60 patients who were admitted to the Primary Children's Medical Center or the University of Utah Medical Center between October 1970 and January 1979. Except for five children from Montana, Oregon, Colorado and Nevada, they all resided in either Utah or Idaho. While three patients cared for during the early 1970's received heparin, none of the others received anticoagulant, antithrombotic or fibrinolytic agents.

From the Division of Pediatric Nephrology, Department of Pediatrics, University of Utah College of Medicine, Salt Lake City.

Submitted, revised, September 2, 1980.

Reprint requests to: Richard L. Siegler, MD, Department of Pediatrics, University of Utah College of Medicine, 50 North Medical Drive, Salt Lake City, UT 84132.

Patients

The average age of our patients was 3 years (range 5 months to 12½ years); 85 percent of the children were younger than 5 years old and 37 percent were between the ages 1 and 2 years (Figure 1).

We detected a seasonal variation, with half of the cases occurring during the summer months (Figure 2).

Prodrome

Almost all the children had diarrhea (93 percent), vomiting (90 percent), or both (84 percent), which preceded the detection of anemia and renal disease by about a week (Table 1). The diarrhea was bloody in about half of the cases, and two patients were referred because ulcerative

ABBREVIATIONS USED IN TEXT
BUN=blood urea nitrogen
CNS=central nervous system
HUS=hemolytic-uremic syndrome

colitis was suspected. Abdominal pain often accompanied the diarrhea, and one patient underwent an appendectomy for suspected acute appendicitis.

A decrease in urinary output was noted by the parents in about half of the children, and pallor or fever was reported during the prodrome in 34 percent and 25 percent of the patients, respectively. While 23 percent of the children had an upper respiratory infection (URI) during the prodrome, its high frequency in the general pediatric population makes an assessment of any causal relationship difficult. In approximately 15 percent of the cases, a seizure preceded admission.

Results

Laboratory Values

All of our patients had proteinuria and hematuria on admission (Table 2). Almost all of them became severely anemic with a hematocrit of less than 25 percent developing in 97 percent; in 85 percent of the children hematocrits were less than 20 percent. Evidence of microangiopathy on blood smears (schistocytes, burr cells) was noted in all cases. Because transfusions were given for hematocrits approximating 15 percent, the potential maximum severity of the anemia could not be estimated. While 75 percent of the children had platelet counts below 100,000 per cu mm, only 10 percent had severe thrombocytopenia (less than 20,000 per cu mm).

Severe azotemia (blood urea nitrogen [BUN] greater than 100 mg per dl) occurred in 72 percent of the cases, and hyperkalemia was common during the oliguric phase (43 percent). Conversely, hypokalemia occurred frequently during the recovery (diuretic) phase (51 percent). Serum uric acid levels exceeded 20 mg per dl in 43 percent of the 23 patients tested.

Clinical Course

In 39 of the children (64 percent) oliguria (less than 240 ml per m^2 per day) developed. In 34 of these 39 anuria (less than 15 ml per day) occurred (Table 3). The mean duration of the anuria was 5.2 days (range 1 to 17), and the combined anuria-oliguria was 8.6 days (range 1 to 23). Dialysis, usually peritoneal, was carried out in 54 percent of the patients. Hypertension was present in 51 percent of the children, and usually occurred only briefly during the first few days in hospital. Late-onset hypertension was infrequent, but was often a presage of severe chronic hypertension. Sixty-four percent of our patients required one or more transfusions with packed

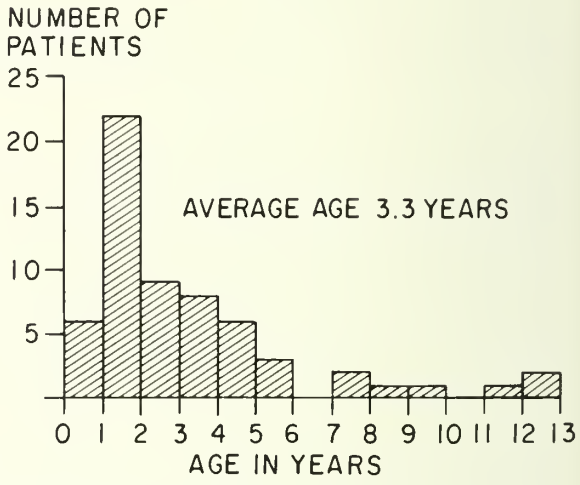


Figure 1.—Age distribution of 60 patients (61 episodes) with hemolytic-uremic syndrome.

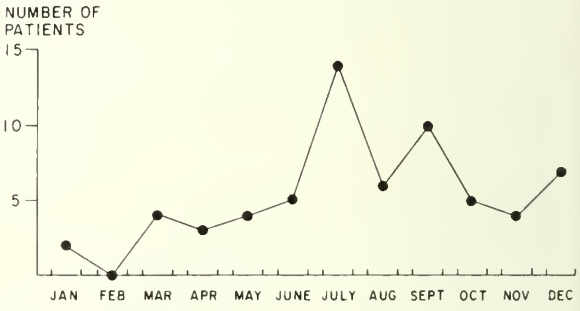


Figure 2.—Seasonal variation in incidence of 61 episodes of hemolytic-uremic syndrome.

TABLE 1.—*Clinical Prodromes Before Admission to Hospital in 60 Patients (61 Episodes) With Hemolytic-Uremic Syndrome*

Prodromes	*Number (Total 61)*	*Percent*
Diarrhea	57	93
With blood	30	49
Vomiting	55	90
Vomiting and diarrhea	51	84
Oliguria-anuria	29	48
Pallor	21	34
Fever	15	25
Upper respiratory infection	14	23
Seizure	9	15

erythrocytes. Seizures occurred during the acute phase of the illness in 24 (40 percent) of the children. However, they were usually generalized and brief, and rarely recurred.

Outcome

Only two patients (3 percent) died during the acute phase of the disease. One other child died two years later, after an unsuccessful renal transplant and chronic hemodialysis (Table 4). One child had a recurrence approximately three years after her first episode. Her initial episode resulted in brain damage and the second in severe chronic hypertension and mild chronic renal failure.

Chronic long-term sequelae were infrequent. Hypertension was still noted in three (5 percent) of the children, in two of them after a year and in a third after five years. Mild renal failure was still present in one of these children after five years. Chronic neurological sequelae (seizures, cortical blindness or psychomotor retardation) persisted in three children (5 percent) at 1, 1½ and 5 years, respectively. Overall, five of the long-term survivors (8 percent) have sustained one or more major sequelae. But, in that different sequelae occurred with recurrence of HUS in the one child, there were major sequelae following six disease episodes in these five patients. One additional child has persistent proteinuria (1+ to 2+), but no other abnormal features. Considering the three children (5 percent) who died, 85 percent of the total number of patients are alive and well with normal values for analysis of urine, blood pressure and renal function, and an absence of neurological abnormalities.

TABLE 2.—*Laboratory Values in 60 Patients (61 Episodes) With Hemolytic-Uremic Syndrome*

Laboratory Values	*Number/Total*	*Percent*
Proteinuria and hematuria	61/61	100
Hematocrit <25%	59/61	97
Hematocrit <20%	52/61	85
Platelet count <100,000 per cu mm	45/61	74
Platelet count < 20,000 per cu mm	6/61	10
BUN >100 mg/dl	44/61	72
K+ >6 mEq/L (oliguric phase)	26/61	43
K+ <3 mEq/L (diuretic phase)	31/61	51
Uric acid >20 mg/dl	10/23	43

BUN = blood urea nitrogen

TABLE 3.—*Clinical Course in 61 Episodes of Hemolytic-Uremic Syndrome*

Clinical Course	*Number (Total 61)*	*Percent*
Oliguria (<240 ml/m²/d)	39	64
Anuria (<15 ml/d)	34	56
Dialysis	33	54
Hypertension	31	51
Transfusion(s)	39	64
Seizure(s)	24	40

TABLE 4.—*Outcome in 61 Episodes of Hemolytic-Uremic Syndrome*

Outcome	*Number (Total 61)*	*Percent*
Deaths	3	5
Early	2	3
Late	1	2
Chronic hypertension	3	5
Chronic renal failure	1	2
Chronic neurological sequelae	3	5
Patients with one or more major sequelae	5	8

Discussion

HUS is not a rare disease, and it is responsible for almost all acute dialysis therapy on our pediatric service. While largely a pediatric disorder, it is also seen in adults, particularly in postpartum women and in women taking oral contraceptives.[2] Moreover, we have been seeing progressively more cases during the last few years, and during the year following this study, we cared for an additional 19 children. Whether this represents a true increase in incidence or merely greater physician awareness is uncertain.

As almost all patients share a common prodrome, the possibility of HUS should be considered in any young patient with diarrhea, especially if accompanied by bloody stools. A falling hematocrit, schistocytes, hematuria and proteinuria should facilitate early diagnosis and avoid injudicious fluid administration and subsequent edema, hyponatremia or both.

While convulsions occurred in 40 percent of our patients, they were not predictive of outcome or central nervous system (CNS) sequelae. Of the seizure episodes, 58 percent were associated with serum sodium concentrations of less than 130 mEq per liter and 13 percent with serum calcium levels of less than 8 mg per dl. There were no episodes of hypertensive encephalopathy. Details of our patients' CNS findings are being reported elsewhere.[6]

As there is good evidence that HUS is a localized intravascular coagulopathy,[2] it is not surprising that anticoagulant, antithrombotic, and fibrinolytic agents have all been used. While it has been suggested that heparin might be helpful,[2,7] there is little evidence of any clear-cut value.[8-11] Similarly, antithrombotic drugs (such as aspirin and dipy-

ridamole) and the fibrinolytic agent streptokinase, appear to be of unproved value or carry an unfavorable risk-benefit ratio.[1] Therefore, we have followed the widely accepted policy of supportive therapy while waiting for spontaneous recovery.[2,7,8]

Unless dehydration is present, fluids are restricted to ongoing losses (insensible, plus urinary and gastrointestinal losses). Because initially most children are essentially anuric, this amounts to 350 ml per m^2 of glucose water a day. If they are also hyponatremic, even less water is given.

Hyperkalemia (potassium greater than 6.0 mEq per liter) is treated with the oral or rectal administration of sodium polystyrene sulfonate (Kayexalate) in doses of 1 gram per kg of body weight. Only rarely are additional measures (such as bicarbonate, glucose with insulin, or calcium) necessary. Because half of our patients became hypokalemic during the recovery phase, we now give generous amounts of potassium once diuresis begins and serum potassium concentrations approach 3 mEq per liter.

Ordinarily, hypertension is easily controlled with intravenously given diazoxide (5 mg per kg of body weight per dose) or intramuscularly given hydralazine (0.2 mg per kg of body weight per dose).

Transfusions with packed erythrocytes (5 to 10 ml per kg of body weight) are generally reserved for children with hematocrits approaching 15 percent. Occasionally they are given earlier, if a gallop rhythm develops. High-output heart failure did not develop in any of the children in our series.

While dialysis has generally been recommended when anuria lasts for more than 24[1,2] or 48 hours,[9,11] we usually do not carry out this treatment in our patients until the BUN concentration exceeds 150 mg per dl, irrespective of the duration of the oliguria or anuria. Exceptions have included uncontrollable or severe hyperkalemia, severe fluid overload or acidosis, or progressive encephalopathy. By following these guidelines, there have been no deaths from a delay in initiating dialysis. Because of its technical simplicity, all but a few older children have been treated with peritoneal dialysis rather than hemodialysis. Peritoneal dialysis is continued for a maximum of 72 hours or until the BUN approaches 50 mg per dl. Most dialysis treatments have lasted between 24 and 48 hours. By withholding protein and only giving fats, carbohydrates and essential amino acids (Amin-Aid, McGaw Laboratories), diuresis almost always begins before the BUN again exceeds 150 mg per dl, and a second dialysis is needed only occasionally. But, because of fluid volume and electrolyte constraints, a negative caloric and nitrogen balance usually occurs in the children for a week or two. Earlier and more frequent dialysis would permit more normal caloric intake and better nutrition. But these advantages need to be weighed against the additional cost and potential morbidity of repeated dialysis. None of our patients have died of infection or any other complication of malnutrition, and mortality and recovery rates compare favorably with those from centers advocating early dialysis.[1,2,7,11]

Very high serum uric acid levels (greater than 20 mg per dl) were found in 43 percent of our patients during the oliguric phase of their illness. This phenomenon, which has previously been reported,[12] did not result in detectable gouty arthropathy or nephropathy, and was not treated with allopurinol.

All 22 patients who did not have oliguria recovered completely. Moreover, surprisingly, we found no difference in the duration of anuria between those who recovered and those left with chronic renal, neurological or hypertensive problems. There was a significant difference, however, (Student's t test, $P < 0.05$) between the number of days of combined anuria-oliguria in those who recovered (8.0 ± 5.5 [1 SD]) and those who sustained chronic renal failure or hypertension (15.3 ± 5.7). This difference, however, was not apparent in those left with only chronic neurological damage. In addition, while 29 of 35 patients (83 percent) with combined anuria-oliguria of 14 days or less recovered completely, only one of four (25 percent) with more prolonged renal failure escaped major sequelae. This relationship between duration of renal shutdown and recovery of renal function has also been noted by others.[4]

None of the 19 additional patients cared for during the year following this study have died; however, one sustained brain damage and another has mild hypertension. Thus, our overall experience indicates that with careful supportive therapy over 95 percent of the children with HUS will survive and approximately 90 percent of survivors will recover completely.

REFERENCES

1. Kaplan BS, Thomson PD, de Chadarevian JP: The hemolytic uremic syndrome. Pediatr Clin N Am 23:761-777, 1976

2. Goldstein MH, Churg J, Strauss L, et al: Hemolytic-uremic syndrome. Nephron 23:263-272, 1979

3. Riella MC, George CRP, Hickman RO, et al: Renal microangiopathy of the hemolytic-uremic syndrome in childhood. Nephron 17:188-203, 1976

4. Dolislager D, Tune B: The hemolytic-uremic syndrome. Am J Dis Child 132:55-58, 1978

5. Sorrenti LY, Lewy PR: The hemolytic-uremic syndrome. Am J Dis Child 132:59-62, 1978

6. Bale JF, Brasher C, Siegler RL: The central nervous system manifestations of the hemolytic-uremic syndrome: Relationship to metabolic alterations and prognosis. Am J Dis Child 134:869-872, 1980

7. Lieberman E: Hemolytic-uremic syndrome. J Pediatr 80:1-16, 1972

8. Kaplan BS, Katz J, Krawitz S, et al: An analysis of the results of therapy in 67 cases of the hemolytic-uremic syndrome. J Pediatr 78:420-425, 1971

9. Gianantonio CA, Vitacco M, Mendilaharzu F, et al: The hemolytic-uremic syndrome. Nephron 11:174-192, 1973

10. Vitacco M, Avalos JS, Gianantonio CA: Heparin therapy in the hemolytic-uremic syndrome. J Pediatr 83:271-275, 1973

11. Upadhyaya K, Barwick K, Fishaut M, et al: The importance of nonrenal involvement in hemolytic-uremic syndrome. Pediatrics 65:115-120, 1980

12. Kaplan BS, Thomson PD: Hyperuricemia in the hemolytic-uremic syndrome. Am J Dis Child 130:854-856, 1976

Allergy and Man's Food History

SOME FOODS ARE more allergenic than others because of mankind's past. If you stop and think about it, prehistoric man has been shown to have been a roving creature that killed small animals, picked berries and dug up roots. He did not raise cows and milk them, he did not have fields of grain and he did not grow sugars. I think that the reason these foods are the most commonly allergenic foods is because they have entered man's diet more recently. Bread is not the staff of life; unfortunately it is in some ways probably one of the worst things going. I think probably one of man's worst discoveries was figuring out how to put yeast with grain. And of course, the growing of grain enabled us to discontinue our nomadic life and to settle in one spot. And by settling in one spot we developed inhalant allergies to the vegetation in the area. Then we grew grain and figured out how to mix the grain with yeast, and we got booze and bread; and we have never been the same since. Some patients just do better on what we call a caveman diet: meats, fruits and vegetables.

—JOHN H. BOYLES, Jr, MD, *Dayton, Ohio*

Extracted from *Audio-Digest Otorhinolaryngology*, Vol. 13, No. 14, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1577 E. Chevy Chase Drive, Glendale, CA 91206.

Refer to: Miller TR, Abele JS, Greenspan FS: Fine-needle aspiration biopsy in the management of thyroid nodules. West J Med 134:198-205, Mar 1981

Fine-Needle Aspiration Biopsy in the Management of Thyroid Nodules

THEODORE R. MILLER, MD; JOHN S. ABELE, MD, *and*
FRANCIS S. GREENSPAN, MD, *San Francisco*

A prospective study was carried out of 136 patients with thyroid nodules. In all of the cases, fine-needle aspiration (FNA) cytology was used in the clinical management. Of the specimens taken, 129 were satisfactory for cytology; 5 were clearly malignant and the diagnosis was confirmed during surgical operation. The diagnosis of follicular neoplasm or "suspicious for malignancy" was made in 29 patients. Operations were done in 21; adenoma was found in 15, cancer in 2 and multinodular goiter in 4. The cases in which a benign diagnosis was made are being followed clinically. From these data and a review of the literature, a plan for the management of patients with thyroid nodules can be outlined. FNA biopsy of the thyroid is an excellent method for eliminating unnecessary operations in patients with thyroid nodules.

THYROID NODULES can be found in approximately 6 percent of the adult population of North America.[1,2] The incidence of thyroid cancer, on the other hand, is about 3.6 per 100,000, or 0.0036 percent.[3] Thus, a high degree of selectivity is essential to prevent unnecessary thyroid operations. Clinical evaluation and studies such as isotope scans and ultrasonography have aided in the selection process, but these techniques are not specific for the diagnosis of thyroid cancer. The development of a simple technique for aspiration biopsy of the thyroid nodule and the use of cytologic analysis of the resulting smears has proved an accurate and reliable method for the preoperative separation of benign from malignant thyroid nodules.[4]

From the Departments of Pathology and Medicine, University of California, San Francisco.

Submitted July 18, 1980.

Reprint requests to: Theodore R. Miller, MD, 595 Health Sciences West, University of California, San Francisco, San Francisco, CA 94143.

Three methods of needle biopsy have been proposed: cutting needle biopsy (CNB) with a Vim-Silverman or Tru-Cut needle, aspiration needle biopsy (ANB) using a 16-gauge needle, and fine-needle aspiration (FNA), utilizing a 22- or 23-gauge needle. FNA has several advantages in that it requires no anesthesia, is nontraumatic, is well accepted by patients and can be repeated as often as necessary. We have used this technique in a prospective study of 136 patients with thyroid nodules. In this report we present the technique of FNA, the criteria for cytologic diagnosis, the results in this series of patients, and an analysis of the present status of FNA in the diagnosis and management of patients with nodular goiter.

Patients and Methods

The patient population consisted of 136 consecutively seen patients referred to one of us (F.S.G.) for evaluation of a thyroid mass. On

ABBREVIATIONS USED IN TEXT

ANB = aspiration needle biopsy
BTN = benign thyroid nodule
CNB = cutting needle biopsy
FN = follicular neoplasms
FNA = fine-needle aspiration

physical examinations one or more thyroid nodules, clearly different from normal thyroid, were seen and isotope scans showed the nodule or nodules to be *cold*. All biopsies were done by the same person (F.S.G.).

The technique of aspiration was that of Löwhagen.[4] The patient lies on his or her back with the neck slightly extended. After cleansing the skin, a 23-gauge needle on a 10-ml syringe in a Cameo syringe holder (Precision Dynamics Corp., 3031 Thornton Ave., Burbank, CA 94504) is inserted into the nodule and with continuous suction the needle is moved quickly back and forth in the nodule. As soon as material is noted in the hub of the needle, the suction is released and the needle withdrawn from the nodule. The needle is then removed from the syringe, the syringe filled with air, and any material in the needle is expelled onto a clean glass slide. A thin smear is made by placing a second slide on top of the first and pulling them apart; one slide is fixed in 95 percent ethyl alcohol and the other air dried. The needle itself is rinsed in a container of Ringer solution, which is later processed by millipore membrane filtration. Air dried slides are stained by Wright stain and alcohol fixed material by a Papanicolaou stain.

Results

Cytology Description

Normal thyroid material was obtained from histologically normal surgical and autopsy specimens. Fine-needle aspiration biopsy of the normal thyroid yields few epithelial cells. The follicular cells occur as single bare nuclei or rare tissue fragments with intact cytoplasm. The chromatin pattern of these lymphocyte-sized nuclei is even, finely divided and dense. When present, the cytoplasm is granular and lacks definitive cell borders.[5]

Nodular goiter (colloid or adenomatous) has a varied cytologic presentation (Figures 1 and 2). Large areas of colloid in a goiter are reflected cytologically by blue-staining waxy material on Wright stain or pink to green material on Papanicolaou stain. The presence of large amounts of colloid is considered characteristic of nodular goiter. If old areas of hemorrhage are sampled, hemosiderin-containing macrophages along with fluid and amorphous debris will dominate the presentation. Follicular structures of various size, from hyperplastic or adenomatous areas, may also be seen. These follicles appear to be three dimensional structures with a top, bottom and sides. Occasionally, large follicles are disrupted and present as a monolayer of rows and columns of uniform evenly spaced nuclei. The nuclei in goiter may show degrees of enlargement up to 2½ times the size of red blood cells and increased amounts of cytoplasm.[4-9]

Chronic thyroiditis has a cytologic presentation (Figure 3) characterized by a heterogeneous population of lymphoid cells similar to those found in a lymph node. These represent the spectrum of cells found in lymphoid aggregates in histological sections of chronic thyroiditis. Epithelial cells with abundant granular cytoplasm, well-defined borders and prominent nucleoli (Hürthle cells) may be present. The lymphoid and epithelial changes in chronic thyroiditis may cause diagnostic errors. Lymphomas may present a similar but more monomorphic pattern. The benign nature of Hürthle cells may not be appreciated due to the unusually large size of the cells.[4-7,9]

Subacute thyroiditis was not encountered in this series. The cytological features of this lesion have been described and correlate with the histological features. Numerous inflammatory cells of lymphocyte origin are present as well as phagocytic cells. The presence of multinucleated giant cells may be of diagnostic importance. These changes are not specific for subacute thyroiditis and clinical correlation is important.[5,7]

Follicular neoplasms (FN) (Figures 4 and 5) are comprised of well-differentiated carcinomas and follicular adenomas. Separation of these two lesions depends on histological examination of the capsule and vessels for invasion by tumor. These features are not sampled by FNA. Smears from these lesions are highly cellular with numerous single cells, cell groups and clusters. A distinctive pattern in FN is the microfollicle. In this monolayer structure, enlarged nuclei are arranged in a circular fashion around a syncytial mass of cytoplasm. This pattern contrasts with the three dimensional structures seen in nodular goiter.

Even though there is overlap between adeno-

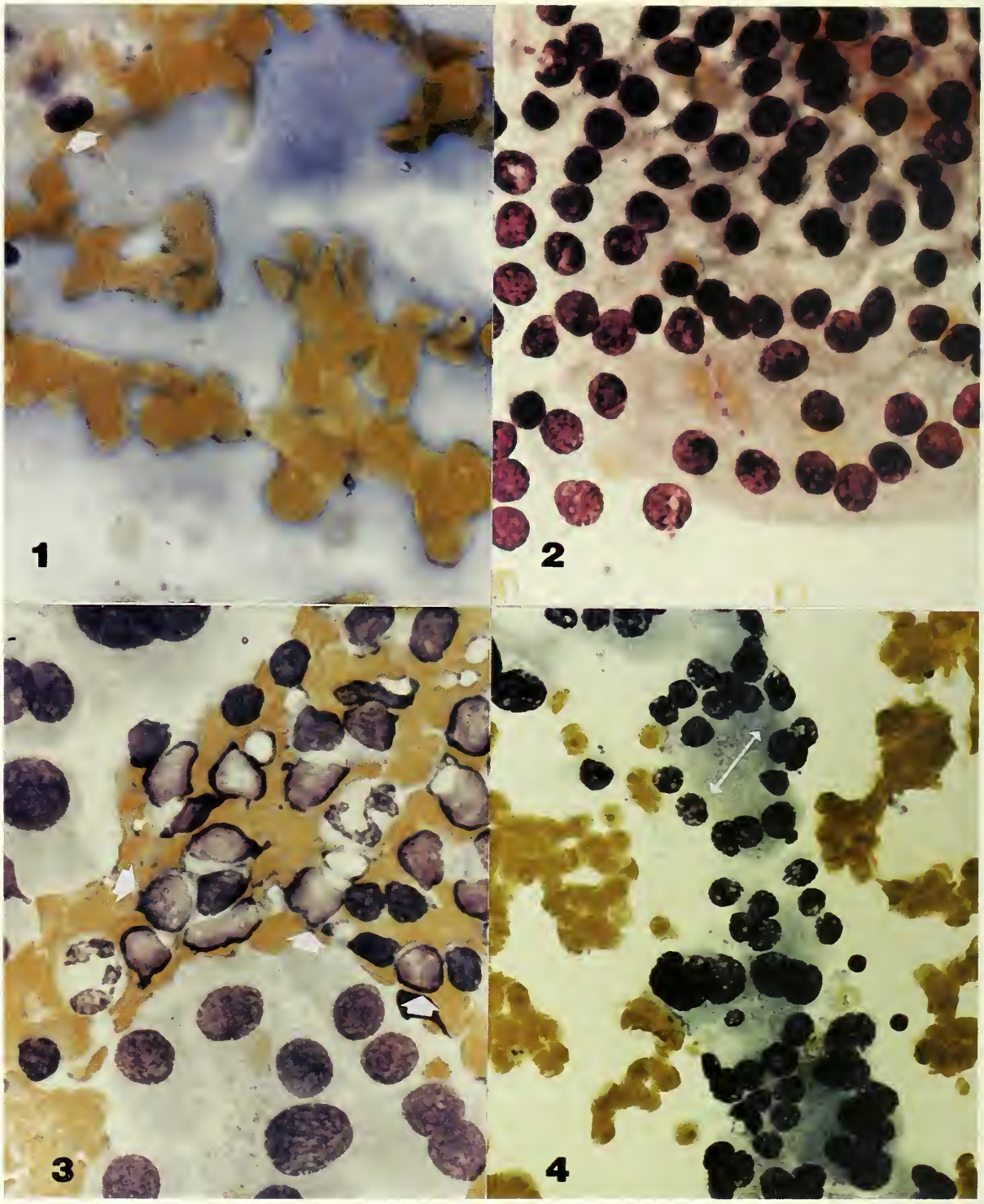


Figure 1.—Nodular goiter. Single bare thyroid nucleus (arrow) mixed with blue colloid and red blood cells. (Wright stain, original 250×.)

Figure 2.—Nodular goiter. Disrupted macrofollicle with small uniform nuclei arranged in rows and columns. (Wright stain, original 250×.)

Figure 3.—Hashimoto disease. Hürthle cells with abundant grey cytoplasm and enlarged nuclei mixed with numerous mature lymphocytes (arrows) and red blood cells. (Wright stain, original 250×.)

Figure 4.—Follicular neoplasm. Notably enlarged nuclei with variability in size. Note arrangement of nuclei in a circular fashion around a syncytial mass of blue cytoplasm (arrow). (Wright stain, original 160×.)

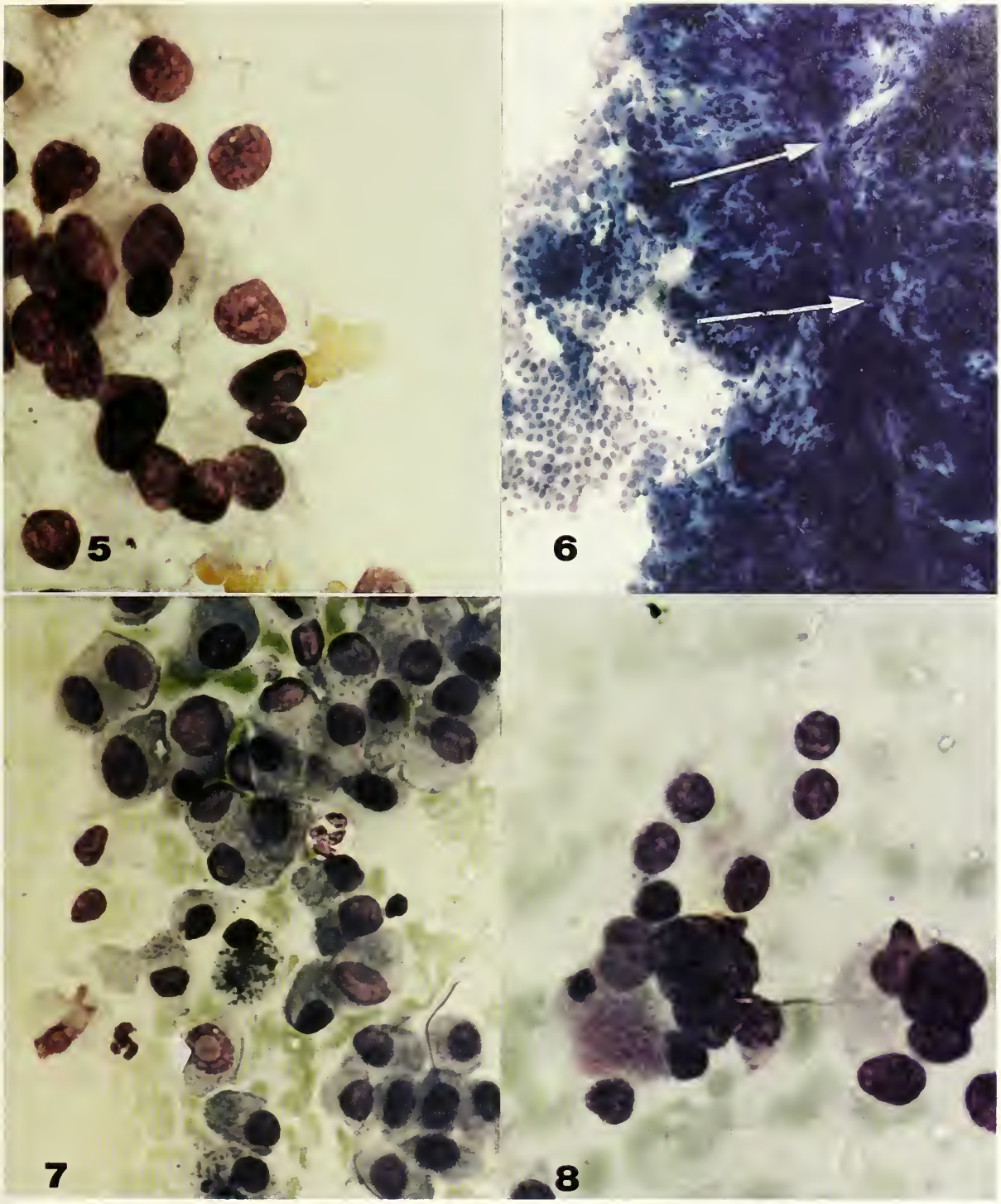


Figure 5.—Follicular neoplasm. Compare the nuclear size with that of the nodular goiter (Figure 2). Note the lack of good cytoplasmic borders. (Wright stain, original 250×.)

Figure 6.—Papillary carcinoma. Abundant epithelial tissue arranged on fibrovascular cores (arrows). (Wright stain, original 63×.)

Figure 7.—Papillary carcinoma. Three features are presented: (1) hypercellularity; (2) nuclear cytoplasmic inclusions (arrow), and (3) distinct cell borders. The nuclei are also larger than those seen in nodular goiter (Figure 2) and most benign follicular neoplasms (Figure 5). (Wright stain, original 160×.)

Figure 8.—Medullary carcinoma. Malignant cell clusters with characteristic intracytoplasmic red granules. (Wright stain, original 250×.)

mas and carcinomas, malignant features can be identified. These features include nuclear enlargement (greater than 90 sq μ), variation in cell and nuclear size and irregularities of the chromatin pattern.[10] Irregular nucleoli are also a feature of follicular carcinoma. A variant of FN is the Hürthle (oxyphilic) cell adenoma and carcinoma which, in addition to the preceding features, has the characteristic features of Hürthle cells.[4-7,9,11]

Papillary carcinoma (Figures 6 and 7) has a more distinctive pattern than follicular carcinoma. Three features, while neither pathognomonic nor uniformly present, are papillary groups, pseudonucleoli and psammoma bodies. Laminated calcified psammoma bodies must be distinguished from the homogeneous spherules of inspissated colloid. Cytoplasmic nuclear inclusions (pseudonuclei) have been found in 90 percent of papillary carcinoma but not in other thyroid neoplasms or diseases. The finding of true papillary groups characterized by delicate blood vessels covered by epithelium is virtually diagnostic. A helpful feature of this tumor is that cytoplasmic borders are sharp and distinct in Wright-stained material, apparent both in single cells and in cell groups. The follicular variant of papillary carcinoma contains features suggestive of a follicular neoplasm, and a diligent search for clues of papillary origin is required.[4-7,9,12,13]

Medullary carcinoma, in addition to single cells and cell clusters with obvious malignant characteristics, offers two distinctive cytologic findings (Figure 8). In the cytoplasm of the malignant cells are finely granulated red granules which are apparent on the Wright-stained material. The second feature is amyloid, which has the appearance of colloid and requires a Congo stain to demonstrate the true nature of this material.[5,9,11]

Analysis and Clinical Data

Satisfactory specimens were obtained in 129 of the 136 patients. The diagnostic categories of FNA cytology diagnosis are listed in Table 1. Benign lesions were diagnosed in 95 patients; the cases of 93 are being followed clinically while thyroxine is being given and 2 patients have been operated upon. One patient had systemic amyloidosis; in the other patient multinodular goiter was diagnosed, and at operation benign follicular adenoma was found. An unequivocal diagnosis of malignancy was made in five patients; all of them were operated upon and the diagnosis, including cell type, was confirmed. In 29 patients there was a diagnosis of "follicular neoplasm" or "suspicious for malignancy"; surgical procedures were carried out in 21. Pathological examination showed follicular adenomas in 15, multinodular goiter in 4 and cancer in 2. One of these latter patients had a follicular variant of papillary carcinoma and the other had Hürthle cell carcinoma. The eight patients in whom operations were not done were in a low-risk category or refused operations. These cases are being followed clinically and thyroxine therapy given.

The incidence of carcinoma in the unequivocally malignant group was 100 percent. When follicular adenomas are included in a group consisting of *malignant, follicular neoplasm* and

TABLE 1.—*Results of Fine-Needle Aspiration Thyroid Biopsy in 129 Patients*

	Fine-Needle Aspiration Cytology Diagnosis	
Benign Lesions	*Follicular Neoplasm or Suspicious*	*Malignant*
Benign thyroid nodule 47	Follicular neoplasm 25	Papillary carcinoma 3
Multinodular goiter 22	Suspicious 4	Follicular carcinoma 1
Cyst 15		Medullary carcinoma 1
Thyroiditis 10		
Normal thyroid 1		
TOTAL 95	29	5
No surgical procedure 93	8	0
Surgical procedure 2	21	5
Corresponding pathological features		
Amyloid 1	Follicular adenoma 15	Papillary carcinoma 3
Follicular adenoma 1	Multinodular goiter 4	Follicular carcinoma 1
	Cancer ..... 2 (Follicular variant papillary carcinoma; Hürthle cell carcinoma)	Medullary carcinoma 1

suspicious, 22 of 26 (85 percent) of the surgical specimens were positive for a neoplasm. Two cases of carcinoma were identified in the follicular neoplasm/suspicious group. The overall incidence of significant pathological findings in patients going to surgery for a suspicious or follicular neoplasm diagnosis was 17 of 21 (81 percent).

The term benign thyroid nodule (BTN) (Table 1) was adopted during the latter portion of this study. The term is used to designate nodules that lack features of primary or metastatic cancer. In most instances these represent dominant nodules in multinodular goiter; however, there may be within this group colloid (macrofollicular) or mixed adenomas. The inclusion of colloid and mixed adenomas into the BTN group is justified in this screening test as it is the more cellular neoplasms (fetal and embryonal) that are felt to have greater potential for capsular or vascular invasion.[14]

Biopsy specimens from seven patients were judged unsatisfactory either because they were too hypocellular for diagnosis or were composed only of peripheral blood. This represents a 95 percent success rate for obtaining a satisfactory cytology specimen.

The correlation of FNA biopsy with the surgical pathological findings is presented in Table 2 and the sensitivity and specificity of FNA biopsy in this series are summarized in Table 3.[15] In an ideal study, all thyroid nodules would have been surgically removed for optimal analysis of the statistical measurements of FNA in thyroid disease. It would be inappropriate to operate on all patients in this series with FNA biopsies showing BTN and undergoing careful clinical follow-up and receiving suppressive therapy. However, with the data available it can be calculated that the sensitivity of the test is 96 percent, and the specificity 20 percent. (Sensitivity is positivity of the test in the presence of disease and the specificity is negativity of the test in health. See Table 3.) Similarly, when correlated with surgical pathological findings, the diagnosis of neoplasm was correct in 85 percent, and the absence of neoplasm was correct in 50 percent. Table 2 shows that all malignant FNA diagnoses were correct. Four multinodular goiters were incorrectly placed in the suspicious or follicular neoplasm group. One macrofollicular adenoma was included in the benign categories. The data on the benign aspirations are limited since very few patients in this category had an opera-

TABLE 3.—*Sensitivity and Specificity of Fine-Needle Aspiration Thyroid Biopsy in This Series*

Pathological Findings at Operation†	Fine-Needle Aspiration Biopsy Diagnosis* *Positive*	*Negative*	*Total*
Positive	22	1	23
Negative	4	1	5
TOTAL	26	2	28

$$\text{Sensitivity} = \frac{\text{True positive}}{\text{Total disease}} \times 100 \quad 22/23 = 96 \text{ percent}$$

$$\text{Specificity} = \frac{\text{True negative}}{\text{Total healthy}} \times 100 \quad 1/5 = 20 \text{ percent}$$

Percent correct positive = $22/26 \times 100 = 85$ percent

Percent correct negative = $1/2 \times 100 = 50$ percent

*For fine-needle aspiration cytology, consider carcinoma or follicular neoplasm positive for neoplasm.

†For surgical pathological findings, consider carcinoma or follicular adenoma positive for neoplasm.

TABLE 2.—*Correlation of Fine-Needle Aspiration Biopsy and Surgical Pathology*

Fine-Needle Aspiration Biopsy		*Pathological Findings at Operation*	
Benign thyroid nodule	2	Follicular adenoma	1
		Amyloid	1
Follicular neoplasm	16	Follicular adenoma	12
		Multinodular goiter	3
		Follicular variant papillary carcinoma	1
Suspicious for carcinoma	4	Follicular adenoma	3
		Multinodular goiter	1
Papillary carcinoma	3	Papillary carcinoma	3
Hürthle cell neoplasm	1	Hürthle cell carcinoma	1
Follicular carcinoma	1	Follicular carcinoma	1
Medullary carcinoma	1	Medullary carcinoma	1
TOTAL	28	TOTAL	28

tion. Thus, specificity and the correctness of diagnosis in the absence of neoplasm can not be realistically determined from this study.

Discussion

Clinical evaluation, thyroid imaging and ultrasound all have been used in determining the malignant potential of thyroid nodules. In each of these tests there is a high degree of sensitivity or positivity in the presence of disease, but the specificity or negativity in the presence of health is low.[15]

In the detection of thyroid neoplasms arising in solitary nodules the highest rate of sensitivity and specificity is achieved by cytohistological methods (FNA/CNB). Reported sensitivity ranges from 66 percent[1] to 93 percent,[9] while specificity varies from 47 percent[9] to 95 percent.[16] Reported series for CNB are not numerous but the sensitivity in two series was 99 percent[9] and 98 percent[17] with a specificity of 100 percent[17] and 45 percent.[9] In contrast, clinical evaluation has a sensitivity of 98 percent[9] but a specificity of only 13 percent.[9] Ultrasound and imaging also offer high sensitivity, 91 percent[18] to 92 percent[19] and 89 percent[20] to 100 percent,[16] respectively; however, the specificity is low, 33 percent[19] to 41 percent[18] for the former and 40 percent[20] to 52 percent[16] for the latter.

The conclusions reached in the various series evaluating thyroid nodules must be carefully examined in view of the authors' different methods and assumptions. For example, it is common for many observers to include adenoma in a benign category. This designation is possible only retrospectively after complete histological examination of the capsule and vessels of the nodule to rule out invasion. Thus, any analysis predicated on data with unspecified follicular neoplasms included in a benign category cannot evaluate the true predictive value of FNA. A second difficulty is that in many series nodules are not examined histologically but the cases are followed clinically for only short periods. Such follow-up raises the sensitivity in that the natural history of most primary thyroid carcinoma even when untreated is protracted. In our series, this type of patient is under long-term care of a single clinician (F.S.G.) so that proper evaluation will be forthcoming.

FNA and CNB are sensitive, specific tests that both contain intrinsic problems that do not allow complete correlation with the histological diagnosis. However, the ease with which these tests are carried out and the accuracy of the results cause them to be indispensible. Malignant disease can be definitely diagnosed in a large percentage of cases and further treatment carried out predicated on a single FNA sample of the nodule. Coupled with the fact that FNA is similar to the drawing of a blood sample and may be done as an outpatient procedure, the patient acceptance is excellent.

Complication rates for FNA and CNB are low. The morbidity of CNB is indicated as being higher than that of FNA. Complications have included hematomas, tracheal puncture and transient laryngeal palsy.[17] FNA has been associated only with minimal hematomas. The observed rate of complications is 1 percent for CNB and less for FNA.[8] Needle-tract implantation by tumor is an unjustified fear as no cases have been reported for 23-gauge needles. A single case of tumor implantation secondary to the use of an 18- to 20-gauge needle has been reported.[21]

The role of FNA biopsy of the thyroid is illustrated in Figure 9. After a careful history and physical examination of the patient, an isotope

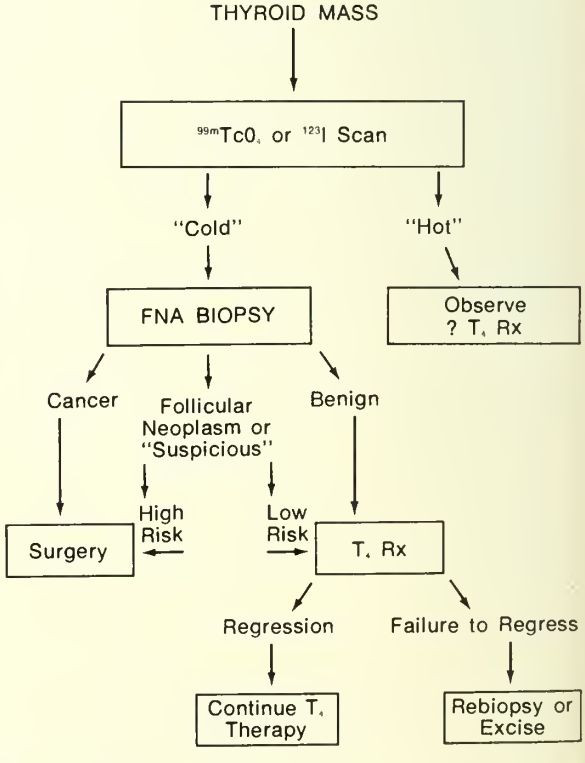


Figure 9.—Decision matrix for management of patients with a thyroid nodule.

scan is done. If the nodule is *hot,* the likelihood of malignancy is small and the patient may be followed. If the nodule is *cold,* FNA biopsy is carried out. If cancer is found, the patient will be referred for surgical operation. If a diagnosis of follicular neoplasm or *suspicious* is made, other risk factors are considered (such as age of patient and size, rapidity of growth and firmness of lesion).[22] If the patient is judged to be at high risk for cancer, an operation is advised; if at low risk, treatment with thyroxine (T_4) is begun. If the cytological diagnosis is benign, the patient is also treated with T_4. Should the lesion fail to regress, or grow while T_4 therapy is being given, then another biopsy study or surgical referral is considered. A similar scheme may utilize the echo scan as the initial screening test.[23]

Cystic lesions of the thyroid are almost always benign.[24] At the time of FNA, the cyst can easily be evacuated. Then material can be obtained from the capsule of any residual mass for cytology. If the cyst continues to recur, surgical excision may be necessary.

In summary, FNA has proved to be an indispensable tool for obtaining a morphological diagnosis of cold thyroid nodules. With experienced clinical judgment, nodules which are shown unequivocally to be benign by FNA need not be surgically excised and therapy for malignant lesions is not needlessly delayed.

Addendum

Since the submission of this manuscript, Kini and colleagues[25] have reported their findings in 1,500 aspirates of cold nodules. Nuclear inclusions were found only in malignant disease. Since our original 136 patients were evaluated, we have examined 400 more, with nuclear inclusions present in 4 of them whose thyroid glands had been exposed to radiation (J. S. Abele, T. R. Miller and F. S. Greenspan: Nuclear inclusions in benign thyroid disease, in preparation).

REFERENCES

1. Stoffer RP, Welch JW, Helwig CA, et al: Nodular goiter—Incidence, morphology before and after iodine prophylaxis and clinical diagnosis. Arch Intern Med 106:10-14, 1960

2. Vander JB, Gaston EA, Dawber TR: Significance of solitary nontoxic thyroid nodules—Final report of 15-year study. Ann Intern Med 69:527-540, 1968

3. Cutler SJ, Scotto J, Devessa SS, et al: Third National Cancer Survey—An overview of available information. J Natl Cancer Inst 53:1565-1575, 1974

4. Löwhagen T, Granberg P-O, Lundell G, et al: Aspiration biopsy cytology (ABC) in nodules of the thyroid gland suspected to be malignant. Surg Clin N Am 59:3-18, 1979

5. Zajicek J: Aspiration biopsy cytology: I. Cytology of supra diaphragmatic organs. Monogr Clin Cytol 4:67-89, 1974

6. Chu E, Hanson T, Goldman J, et al: Study of cells in fine-needle aspiration biopsy of the thyroid gland. Acta Cytologica (Baltimore) 23:309-314, 1979

7. Crockford PM, Bain GO: Fine-needle aspiration biopsy of the thyroid. Can Med Assoc J 110:1029-1032, May 4, 1974

8. Schnürer LB, Widström A: Fine-needle aspiration of the thyroid gland—A cytological comparison in cases of goiter. Ann Otol Rhinol Laryngol 87(2 pt. 1):224-227, Mar-Apr 1978

9. Hamburger JI, Miller JM, Kini SR: Clinical-pathological Evaluation of Thyroid Nodules, Handbook and Atlas. Southfield, Mich., Northland Thyroid Publishing Co., 1949 Ltd. Ed.

10. Boon ME, Löwhagen T, Willems J-S: Planimetric studies on fine-needle aspirates from follicular adenoma and follicular carcinoma of the thyroid. Acta Cytologica (Baltimore) 24:145-148, 1980

11. Löwhagen T, Sorengen E: Cytologic presentation of thyroid tumors in aspiration biopsy smear—A review of 60 cases. Acta Cytologica (Baltimore) 18:192-197, 1974

12. Christ ML, Haja J: Intranuclear cytoplasmic inclusions (invaginations) in thyroid aspiratons: Frequency and specificity. Acta Cytologica (Baltimore) 23:327-331, 1979

13. Chen KTK, Rosa J: Follicular variant of thyroid papillary carcinoma:: A clinical pathological study of six cases. Am J Surg Path 1:123-130, 1977

14. Crocker DW: The thyroid gland, chap 18, *In* Coulson WF (Ed): Surgical Pathology, Vol. 2. Philadelphia, PA, J.B. Lippincott Co., 1978, pp 806-836

15. Galen RS, Gambino SR: Beyond Normality: The Predictive Value and Efficiency of Medical Diagnosis. New York, John Wiley and Sons, 1975

16. Einhorn J, Franzen S: Thin-needle biopsy in the diagnosis of thyroid disease. Acta Radiologica (Stockholm) 58:321-336, 1962

17. Wang C, Vickery A, Maloog F: Needle biopsy of the thyroid. Surg Gynecol Obstet 143:365-368, 1976

18. Miskin M, Rosen LB, Walfish PG: B-Mode ultrasonography in assessment of thyroid gland lesions. Ann Intern Med 79:505-510, 1973

19. Walfish PG, Hazani E, Strawbridge HT, et al: Combined ultrasound and needle aspiration biopsy in the assessment of hypofunctioning thyroid nodule. Ann Intern Med 87:270-274, Sep 1977

20. Grosenbeck HP: Evaluation of routine scintiscanning of nontoxic thyroid nodule—I. The preoperative diagnosis of thyroid carcinoma. Cancer 12:1-5, 1959

21. Sinner WN, Zajicek J: Implantation metastasis after percutaneous transthoracic needle aspiration biopsy. Acta Radiol [Diagn] (Stockh) 17:473-479, 1976

22. Greenspan FS: Thyroid nodules and thyroid cancer. West J Med 121:359-365, 1974

23. Blum M, Pasalaqu A: Managing the solitary thyroid nodule: Echography's role. Hosp Pract 13:65-72, 1978

24. Clark OH, Okerlund MD, Cavalieri RR, et al: Diagnosis and treatment of thyroid, parathyroid and thyroglossal duct cysts. J Clin Endocrinol Metab 48:983-988, 1979

25. Kini SR, Miller JM, Hamburger JI, et al: Cytopathology of papillary carcinoma of the thyroid by fine-needle aspiration. Acta Cytologica (Baltimore) 24:511-521, 1980

Refer to: Sharlip ID: Penile revascularization in the treatment of impotence. West J Med 134:206-211, Mar 1981

Penile Revascularization in the Treatment of Impotence

IRA D. SHARLIP, MD, *San Francisco*

New clinical developments in the diagnosis and treatment of male sexual dysfunction have occurred in the past several years. Much of this information has not been disseminated to the general medical public. Of particular note, a series of reliable penile prosthetic devices for the treatment of advanced erectile dysfunction is now considered to be established and valid surgical therapy.

The new diagnostic techniques of nocturnal penile tumescence monitoring, penile plethysmography, penile sphygmomanometry and phalloarteriography are beginning to show that some patients with erectile impotence have arteriosclerosis of the penile arteries. These patients were formerly considered to have psychogenic or idiopathic impotence. Some of these patients with vasculogenic impotence may benefit from the new surgical technique of penile revascularization, thus obviating the need for penile prosthetic implants.

A preliminary report of a small series of cases of corpus cavernosum revascularization using the microsurgical implantation of the inferior epigastric artery directly into the corpus cavernosum with prolonged systemic anticoagulation gives a cure/improvement rate of 40 percent. Better selection of patients for operation and perfection of surgical technique offer the chance for improvement in this rate of success. The proper role of corpus cavernosum revascularization in the treatment of impotence remains to be clearly defined. However, these preliminary results, coupled with several reports from Europe, are sufficiently encouraging to justify continued clinical investigation and surgical experience with penile revascularization for vasculogenic impotence.

SCIENTIFIC INTEREST and research in male reproductive physiology have been limited until recently and are only now beginning to establish a foothold of respectability with the lay and medical public. Curiously, this lack of interest has occurred despite universal cultural emphasis on fertility and male sexual prowess. Search for improvement or preservation of sexual powers dates to time immemorial[1] and, even today, folk tales and folk medicine throughout the world are replete with sexual witchcraft and home remedies. For example, the reputed aphrodisiac power of powdered rhinoceros horn is causing widespread poaching and the threatened extinction of rhinoceroses in Africa and India; "cell therapy" is used in Germany for sexual rejuvenation, pur-

Dr. Sharlip is in private practice and Clinical Assistant Professor of Urology, University of California, San Francisco, School of Medicine.

Submitted, revised, August 12, 1980.

Reprint requests to: Ira D. Sharlip, MD, 3838 California Street, Suite 408, San Francisco, CA 94118.

ABBREVIATIONS USED IN TEXT
CCR = corpus cavernosum revascularization
EC = epigastricocavernostomy
IEA = inferior epigastric artery

portedly induced by the subcutaneous implantation of fetal testis cells from lambs into humans; and a Chinese herbal medicine called Seahorse Genital Tonic Pills, composed of such ingredients as seahorse, ginseng, horse penis and testis, antler, tiger bone, deer sinew and gecko, is sold in San Francisco for "strengthening the genital functions."

Legitimate sexual medicine has made significant advances recently both in Europe and in the United States. Many of these advances have important clinical relevance but have yet to be disseminated to the medical public.

Of particular note, the 1970's saw the development of a series of surgically implanted penile prostheses for the treatment of organic impotence. The semirigid rod prosthetic device (Small-Carrion, Finney and others) and the inflatable prosthetic device have restored sexual function to thousands of men with advanced erectile dysfunction and have been accepted now as established and valid surgical therapies. Penile prosthetic implantation, however, is not a happy solution for all impotent patients. Some men with incomplete, yet incapacitating, organic impotence—and some with total impotence—consider implantation of prosthetic materials, and the frequent concomitant destruction of any remaining erectile capacity,[2] objectionable and unacceptable.

The new diagnostic techniques of nocturnal penile tumescence monitoring, penile sphygmomanometry, penile plethysmography and phalloarteriography are beginning to show that many men previously thought to have psychogenic or idiopathic impotence actually have vasculogenic impotence due to arteriosclerotic obstruction of the small vessels in the internal pudendal or penile arterial tree, or both. Further support for the new concept of arteriosclerosis of the penile vessels comes from the studies of Ruzbarsky and Michal,[3] who showed the occurrence of fibrosis and calcification of the intima and media and luminal narrowing of the penile arterial tree related to aging and diabetes, and of Benson and co-workers,[4] who have shown that penile "polsters" are probably arteriosclerotic structures that occur with aging. The incidence of penile arteriosclerosis is unknown, but current estimates without statistical basis are that perhaps 25 percent of impotent patients have small-vessel vasculogenic impotence.

Some patients with penile arteriosclerosis may be helped by a new surgical technique, corpus cavernosum revascularization (CCR), which avoids the use of prosthetic devices. Surgical revascularization of the corpus cavernosum has the potential to increase penile blood flow sufficiently to allow improvement in erectile function and resumption of sexual intercourse. The concept of revascularizing the corpus cavernosum for vasculogenic impotence was originated in Prague, Czechoslovakia, by V. Michal.[5] The theoretical basis of the operation is to increase basal penile blood flow to just below the threshold value necessary to initiate erection. This threshold has been shown by Michal to be approximately 93 ml per minute.[5] Then, with further sexual stimulation, the patient's own remaining capacity to increase penile blood flow, even if reduced, adds sufficient flow to exceed the threshold value and create an erection. Once achieved, the erection should be maintained, since the flow required for maintenance of erection is about half that required for initiation of erection.[5]

Corpus cavernosum revascularization is appealing to many patients because it offers the chance to achieve normal innate erections without the use of prosthetic materials and without long-term risks, even in the event of operative failure. A variety of surgical techniques to revascularize the corpus cavernosum have been used. These include direct anastomosis of the inferior epigastric artery (IEA) to the corpus cavernosum or epigastricocavernostomy (EC), saphenous or basilic vein graft between the IEA and corpus cavernosum and similar venous grafts from the femoral artery to the corpus cavernosum. The latter technique, using the femoral artery as the source of blood flow, has been associated with priapism, due to excess blood flow, and surgical failure. Recently, Michal has carried out an end-to-side microsurgical anastomosis of the IEA to the dorsal penile artery when phalloarteriography showed that the arteriosclerotic block was proximal to the bifurcation of the dorsal and deep penile arteries.[6]

American experience with CCR has been disappointing.[7-10] American surgeons have used a variety of techniques in small series so that intimacy with surgical technique has not been developed here. In general, microsurgical technique and prolonged systemic anticoagulation have not been

used. Because of poor results, the value of CCR has been doubted in the United States.

European results have been more encouraging. Ginestié, of Montpellier, France, using direct epigastrico-cavernostomy in 50 patients, has reported 50 percent to 60 percent functional success in resuming sexual intercourse[11,12] and attributes his success to surgical experience, microsurgical technique and the use of systemic anticoagulation before, during and after surgical operation (Ginestié J, personal communication, March 1979). Michal's initial report of microsurgical direct EC included 21 patients.[5] Eight of the procedures were technical failures. However, of the 13 patients in whom patent anastomosis was achieved, nine resumed normal sexual activity. Sarramon, from Toulouse, France, reported on 14 patients treated by anticoagulated microsurgical direct EC with surgical success in eight.[13]

In an effort to duplicate these better results, a series of microsurgical anticoagulated direct epigastricocavernostomies has been undertaken The following is a preliminary report of the first five cases in that series.

Patients and Methods

Patients referred with a diagnosis of impotence were evaluated initially by detailed medical and sexual history and physical examination. Particular emphasis was paid to examination of the abdomen, genitalia, prostate, rectal sphincter tone, perianal sensation, bulbocavernosus reflex, femoral and lower extremity pulses and neurological examination. Water or gas cystometry (or both) was then done. Laboratory evaluation included analysis of urine, examination of expressed prostatic secretions, complete blood count, serum creatinine and two-hour postprandial blood glucose determinations, liver function tests, thyroid function tests, and serum testosterone, follicle stimulating hormone, luteinizing hormone and prolactin studies. Psychological testing using the Minnesota Multiphasic Personality Inventory and nocturnal penile tumescence monitoring were done in most cases to rule out psychogenic impotence. Psychiatric evaluation was done when appropriate. Penile systolic blood pressure measurements were obtained using the Doppler technique. On both sides of the penis the Doppler probe was placed dorsally for the dorsal artery, laterally for the deep artery, ventrally adjacent to the urethra for the spongiosal artery and over the glans for the glans artery. Thus, a total of eight measurements was possible in each case. In most cases, all eight arteries were not audible. The average penile systolic pressure was taken as the average of the audible pulses.

This protocol eliminated from consideration patients with impotence with obvious endocrine, traumatic, pharmacologic, psychogenic, neurogenic and surgical causes. The remaining patients were considered to have vasculogenic or idiopathic impotence. If the ratio of penile to brachial systolic blood pressure was below 0.8,[14] or the

TABLE 1.—*Preoperative Evaluation of Patients*

Patient	*Age*	*Cause of Impotence*	*Duration of Impotence*	*NPTM*	*Penile/Brachial Systolic Blood Pressure*	*Penile Arteriogram*
1	27	Diabetes	2 years	Abnormal	103/130=0.79	Abnormal
2	63	Peripheral vascular disease	11 years	Abnormal	100/170=0.59	Abnormal
3	71	Diabetes	12 years	Abnormal	108/170=0.64	Abnormal
4	50	Penile vascular disease	2 years	Abnormal	85/110=0.77	Abnormal
5	33	Diabetes	3 years	Abnormal	124/125=1.00	Abnormal

NPTM=nocturnal penile tumescence monitoring

TABLE 2.—*Operative and Postoperative Results of Epigastricocavernostomy*

Patient	*Flow in IEA (ml/min)*	*Intra-operative Erection (percent)*	*Complications*	*IEA by Doppler Examination Postoperatively*	*Postoperative Condition*
1	60	50	IEA thrombosis-declotted, repeat anastomosis done within 24 hours	Patent	80 percent normal 0 to 3 months; then 50 percent normal 3 to 12 months; improved, fair functional success
2	15	None	None	Patent	No improvement
3	20	None	Wound infection	Not patent	No improvement
4	..	50	None	Patent	No improvement
5	75	50	None	Patent	90 percent normal 0 to 6 months

IEA=interior epigastric artery

ratio of penile to mean brachial pressure was below 1.0, the possibility of vasculogenic impotence was considered and penile arteriography was done using the technique of Ginestié.[15]

Those patients with distinctly abnormal internal pudendal or penile arteriograms were then given a diagnosis of vasculogenic impotence due to small-vessel disease in the internal pudendal or penile arterial tree. They were offered a choice of surgical alternatives, including semirigid rod prosthetic implant, inflatable penile prosthetic device and corpus cavernosum revascularization. The latter was offered only if the common iliac, external iliac and inferior epigastric arteries were normal on the arteriogram. Diabetes was not considered a contraindication to CCR if the patient had no evidence of peripheral or autonomic neuropathy, normal antegrade ejaculation, normal rectal sphincter tone, normal perianal sensation, normal bulbocavernosus reflex and a normal cystometrogram.

Corpus cavernosum revascularization was accomplished by direct epigastricocavernostomy, using microsurgical technique and systemic anticoagulation. The IEA was exposed through a paramedian incision and isolated up to the level of the umbilicus, where it was transected. It was then brought through the incision in the anterior rectus fascia and passed through a subcutaneous tunnel to the base of the penis. A second short incision at the lateral penile base was used to expose the dorsolateral tunica albuginea. A plug of tunica albuginea was excised and a microsurgical anastomosis of the inferior epigastric artery to the endothelium of the corpus cavernosum was constructed using sutures of 9-0 nylon. Extremely delicate handling of all tissues and detailed attention to the principles of microsurgery were observed at all times. When the anastomosis was complete, the penis was observed for the occurrence of a partial erection lasting several minutes. The wounds were then closed in standard fashion. Anticoagulation was carried out with subcutaneous administration of heparin preoperatively and for four days postoperatively. Therapy was then changed to administration of crystalline warfarin sodium (Coumadin) for six months. The average length of stay in hospital in the uncomplicated cases was eight days.

Results

Five patients with vasculogenic impotence requested corpus cavernosum revascularization. Tables 1 and 2 give the clinical data of these five cases. Figure 1 represents a normal arteriogram of the penile vessels. Figures 2 and 3 are the abnormal penile arteriograms of two patients in this series showing typical stenoses of the penile arteries. The patients' ages ranged from 27 to 71. Preoperatively, patients 2 and 3 were totally impotent, while patients 1, 4 and 5 could achieve 25 percent of normal erectile size and rigidity for short periods of time. All five patients were unable to achieve vaginal penetration. Three patients had diabetes without evidence of neurogenic

Figure 1.—Normal left phalloarteriogram in right posterior oblique position showing normal appearance of dorsal and deep penile arteries. Distal portion of deep artery is frequently not visualized. Note absence of stenosis and amputation of arteries. Note Foley catheter in urethra. Penis points to patient's right with glans penis at left margin of figure.

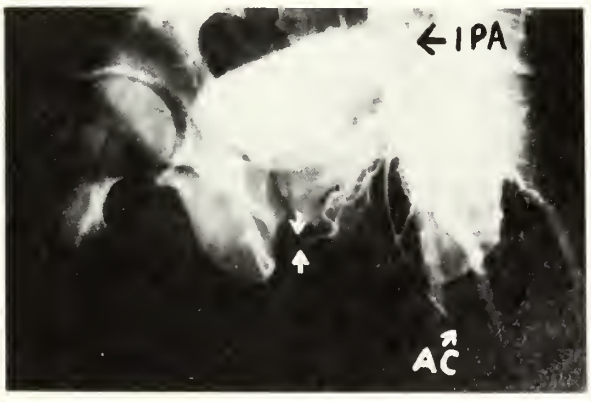


Figure 2.—Abnormal left phalloarteriogram in right posterior oblique position from patient 1 showing amputation of both dorsal and deep penile arteries (arrows). IPA indicates internal pudendal artery leading to penile artery and its branches. AC is arterial catheter.

Figure 3.—Enlarged view of abnormal right phalloarteriogram in left posterior oblique posterior position from patient 4 showing pronounced stenosis of deep penile artery (arrow) and dorsal artery of diminished caliber. Diagonal white line is the arterial catheter.

impotence, one patient had widespread peripheral vascular disease and one patient had idiopathic penile vascular disease. The duration of impotence ranged from 2 to 12 years.

Blood flow in the inferior epigastric artery was measured in four of the five cases. This was done in the operating room by direct measurement before anastomosing the IEA to the corpus cavernosum. Liberal topical administration of lidocaine (Xylocaine 2%) helped to prevent vasospasm in the IEA. In the two cases with blood flow of 50 ml per minute or greater, a transient partial erection was observed immediately following the anastomosis. These were the two cases in which there was functional success postoperatively. The first patient had a flow of 50 ml per minute in the operating room and resumed sexual intercourse two weeks after the operation, with erection estimated to be 80 percent of normal. There was then a gradual decline to 50 percent of normal at a year after operation, allowing the patient intermittent functional success with intercourse. Patient 5 had a blood flow of 75 ml per minute in the IEA during the surgical procedure. He also had a 50 percent erection in the operating room immediately following the anastomosis and has resumed sexual intercourse. He states that his erections are 90 percent of normal. The length of postoperative follow-up in this case is six months at present. Patient 4 also had a partial erection in the operating room, but blood flow in the IEA was not measured. There was no improvement in erections postoperatively. Two patients had blood flow below 50 ml per minute. Neither patient had an intraoperative erection following anastomosis, and neither patient benefited from the surgical procedure. There were two surgical complications in the five patients. In the first patient in the series, thrombosis of the transplanted IEA was diagnosed by absence of audible Doppler pulse and by arteriography 24 hours after operation. The patient was returned to the operating room immediately. The anastomosis was taken down, and the artery was declotted with a small Fogarty catheter. A flow of 60 ml per minute was then obtained from the artery. The anastomosis was redone at another site nearby on the corpus cavernosum. In patient 3 a major wound infection developed which responded to prolonged local wound care. Priapism did not occur in any case.

Discussion

Although anatomically suitable, patients 2 and 3 were probably poor candidates for successful corpus cavernosum revascularization because they were chronologically over age 60, had chronic systemic disease making them physiologically even older and had been totally impotent for more than ten years. In both cases, the surgical procedures failed. In both cases, intraoperative flow in the IEA was very poor, and no erection occurred immediately following the anastomosis, possibly predicting functional failure of the operation. It is thought that a flow of 45 to 160 ml per minute is necessary to initiate erection.[5] Blood flow in the normal IEA is 20 to 120 ml per minute,[5] making it suitable as a source of basal blood flow upon which the patient's remaining innate flow can add to produce erection with sexual stimulation. Thus, a baseline flow in the IEA of 50 ml per minute seems to be important for success of epigastricocavernostomy. That concept is borne out in this small series. The two cases in which the flow was 15 and 20 ml per minute were failures, while the two in which flow was greater than 50 ml per minute resulted in definite improvement in erection. Further experience with the reliability of intraoperative IEA flow as a predictor of functional success or failure of epigastricocavernostomy is needed. Also, a method of measuring flow in the IEA preoperatively might be helpful to proper case selection for CCR using the IEA.

The question of whether patients with diabetic impotence should be excluded from candidacy for CCR has not been answered. Many investigators have excluded diabetic patients because of the potential coexistence of neurogenic as well as vasculogenic impotence. In this series, the diagno-

sis of vasculogenic impotence, based on low penile blood pressure and abnormal penile arteriograms, was felt to be secure. The absence of any signs or symptoms of neuropathy, as well as a normal cystometrogram, were taken as sufficient evidence that there was no neurogenic component, and these patients were then included in the surgical group. Of the three diabetic patients, one with only short-term follow-up is cured, one with longer term follow-up was improved and one was a failure. The latter was one of the patients with poor IEA blood flow. These results indicate that diabetic patients should not be excluded from consideration as possible candidates for CCR.

Looking at the entire series, the cure/improvement rate is two of five, or 40 percent. If the two older patients with poor flow in the IEA are eliminated as poor candidates who perhaps should not have been considered for operation in the first place, the cure/improvement rate in the three remaining patients is 67 percent. Corpus cavernosum revascularization is attractive to patients because it offers a chance to regain natural erections without the use of prosthetic material. Should it fail, implant surgical procedures can then be done; these are not precluded by a previous attempt at CCR. The use of microsurgical technique and perioperative heparin administration followed by at least six months of crystalline warfarin sodium therapy may significantly improve the results of CCR, as claimed by Ginestié. Surgeons trained in microsurgery will rapidly appreciate the advantages of microsurgical technique in dealing with an artery, such as the distal IEA, with a diameter of 1 to 2 mm. This surgical procedure is tedious, requiring much attention to fine detail and ample microsurgical experience.

Conclusion

As increasing experience is gained with CCR, its proper role in the treatment of erectile dysfunction will become more clearly defined. Penile revascularization may have its greatest applicability for those patients with partial, but inadequate, erections who still have enough penile blood flow remaining with sexual stimulation to produce an erection when added to the increased basal flow resulting from this operation. Many of these patients are initially unwilling to proceed to prosthesis implantation. Perhaps CCR will be helpful to these patients until such time as the basal plus stimulated penile flow deteriorates below the threshold for erections. These patients may then proceed to prosthetic implantation, which is not compromised by the previous revascularization surgical procedures. In the meantime, it is possible that they will have gained a reasonable period of adequate sexual function without the use of prosthetics. This role for CCR is, of course, speculative and remains to be validated by subsequent experience.

At present, immediate requirements in this field are for (1) basic and clinical research to improve our knowledge of the physiology of erection, (2) research into the hemodynamics and morphology of penile revascularization and (3) perfection of surgical techniques that will allow creation of long-term patent vascular anastomosis of the donor vessel and corpus cavernosum.

As further experience with CCR is gained, it is reasonable to expect initial technical and functional results to improve with refinement of surgical indications and technique. The initial results of this small series, coupled with several reports from Europe, are sufficiently encouraging to justify continued clinical investigation and surgical experience with penile revascularization for vasculogenic erectile dysfunction epigastricocavernostomy.

REFERENCES

1. Gee WF: A history of surgical treatment of impotence. Urology 5:401-450, 1975

2. Scott FB, Byrd GJ, Karacan I, et al: Erectile impotence treated with an implantable inflatable prosthesis. JAMA 241: 2699-2612, 1979

3. Ruzbarsky V, Michal V: Morphologic changes in the arterial bed of the penis with aging. Invest Urol 15:194-199, 1977

4. Benson GS, McConnell J, Lipshultz LI: Penile "Polsters"—Normal functional structures or arteriosclerotic changes? Presented at the Seventy-Fifth Annual Meeting, American Urological Association, May 21, 1980

5. Michal V, Kramar R, Pospichal J, et al: Arterial epigastricocavernous anastomosis for the treatment of sexual impotence. World J Surg 1:515-520, 1977

6. Michal V: Revascularization procedures of the cavernous bodies. Presented at the First International Conference on Corpus Cavernosum Revascularization. New York, Oct 1978

7. Zorgniotti AW: Invited commentary. World J Surg 2:247-248, 1978

8. Leveen HH: Experiences and techniques utilized to revascularize the penis. Presented at the First International Conference on Corpus Cavernosum Revascularization. New York, Oct 1978

9. Casey WC: Revascularization of corpus cavernosum for erectile failure. Urology 14:135-139, 1979

10. Zorgniotti AW, Padula G, Rossi G: Impotence caused by pudendal arteriovenous fistula. Urology 14:161-162, 1979

11. Ginestié J, Romieu A: Traitement des impuissances d'origine vasculaire: La revascularisation des corps caverneux. J d'Urol et de Nephrol 82:853-859, 1976

12. Ginestié J, Ginestié JF, Romieu A: Arteriographie des arteres honteuses internes: Revascularisation des corps caverneux dans les impuissances d'origine vasculaire. J d'Urol et de Nephrol 82(Suppl 2):509-510, 1976

13. Sarramon JP, Leandri P: Corpus cavernosum revascularization: Results in fourteen cases. Presented at the First International Conference on Corpus Cavernosum Revascularization. New York, Oct 1978

14. Engel G, Burnham SJ, Carter MS: Penile blood pressure in the evaluation of erectile impotence. Fertil Steril 30:687-690, 1978

15. Ginestié JF, Romieu A: L'Exploration Radiologique de L'Impuissance. Paris, Maloine, 1977

CASE REPORTS

Refer to: Schmidt CA, Gordon R, Ahn C: Bronchogenic cyst presenting subsequent to intrapleural rupture. West J Med 134:212-214, Mar 1981

Bronchogenic Cyst Presenting Subsequent to Intrapleural Rupture

CARLOS A. SCHMIDT, MD
ROBERT GORDON, MD
CHANGWOO AHN, MD
Fontana, California

CONGENITAL BRONCHOGENIC CYSTS are a relatively common malformation. Although described in 1769 by Morgagni,[1] the first attempt to classify these lesions was in 1880 by Grawitz.[2] Koontz (1925)[3] collected 108 cases and Bowden (1948)[4] described their occurrence in fetuses. Both of these series concluded that the incidence in males and females is the same, and although most bronchogenic cysts are found in children in the first decade of life,[5] they have been found in elderly populations as well. They occur bilaterally in 25 percent of cases, on the left side in 50 percent and on the right side in 25 percent. Maier (1948)[6] classified mediastinal bronchogenic cysts according to the location as paratracheal, carinal, hilar and esophageal. The hilar type is the most common form.

The differential diagnosis includes the following: lymphoma, neurogenic tumors, teratomas, thymoma, duplication cysts of the esophagus and aneurysm of the aorta. The usual clinical presentation is that of a mass lesion, noted on a routine x-ray study of the chest, in an otherwise asymptomatic patient. The complications, although rare, consist of (1) compression of the airway with or without respiratory difficulty[6,7] (dyspnea appears more often in the subcarinal type in neonates)[8]; (2) secondary infection, usually producing an irritating nonproductive cough (mostly in adults)[6,8,9] or repeated respiratory infection (bronchiectasis in right upper lobe) due to a compression of a portion of the bronchial tree[6,10]; (3) dysphagia (compression of esophagus)[6,10-13]; (4) rupture into other structures such as lung, trachea and esophagus, with possible hemorrhage and hemoptysis with or without fistulous tract[11,14]; (5) malignant changes[11,15,16] and (6) cardiac compression and tamponade due to a large intrapericardial cyst.[17]

In addition to these, we report the rupture of an infected bronchogenic cyst into the pleural cavity, with associated symptoms of pleurisy and empyema.

Report of a Case

A 15-year-old girl was admitted to Kaiser Foundation Hospital in Fontana, California, on August 21, 1979, with a four-day history of right-sided chest pain, persistent temperature of 38.9°C (102°F) and dysphagia. Her past history was noncontributory, and she stated that she had had no previous symptoms. A complete physical (without an x-ray study of the chest) had been done three months earlier and indicated the patient to be in good health. Evaluation at this time included an x-ray study of the chest that showed a rounded mediastinal mass (4 to 5 cm) on the right side (Figure 1). Further fluoroscopic studies using barium taken orally as the contrast medium, indicated a dilatation of the esophagus above the T-5 and T-6 level, with pronounced narrowing below this level. The esophagus was compressed posteriorly and from the right, just below the tracheal bifurcation (Figure 2). A right-sided posterolateral thoracotomy was done on August 24. On entering the right pleural space, extensive reaction was noted, consisting of a fibrinous exudate and 350 ml of purulent fluid. A 4 by 4 by 3 cm mediastinal mass was identified. On its anterolateral surface an area of necrosis with a 0.6 cm perforation was noted. This site communicated with the right pleural space. The mass was excised

From the Department of Surgery, Southern California Permanente Medical Group, Fontana.

Submitted March 20, 1980.

Reprint requests to: Changwoo Ahn, MD, Department of Surgery, Southern California Permanente Medical Group, Fontana, CA 92335.

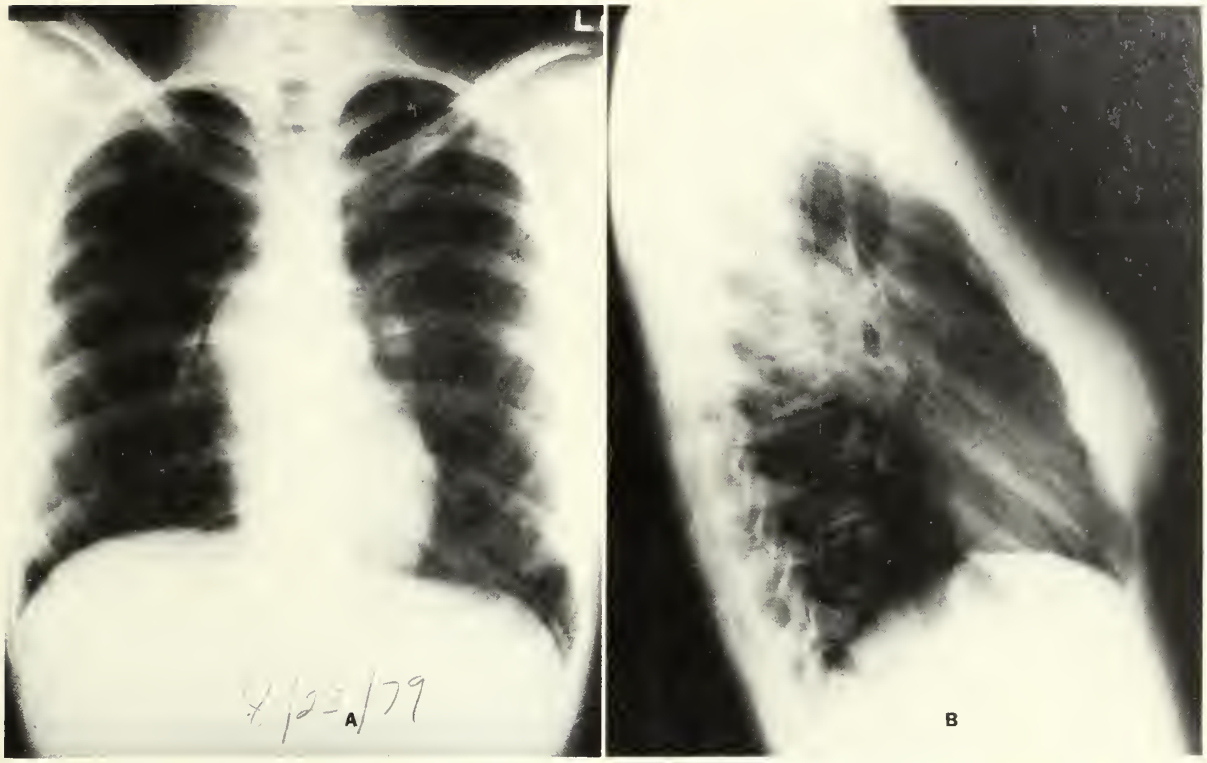


Figure 1.—A & B, Posteroanterior and lateral views of the chest; right-sided midmediastinal mass.

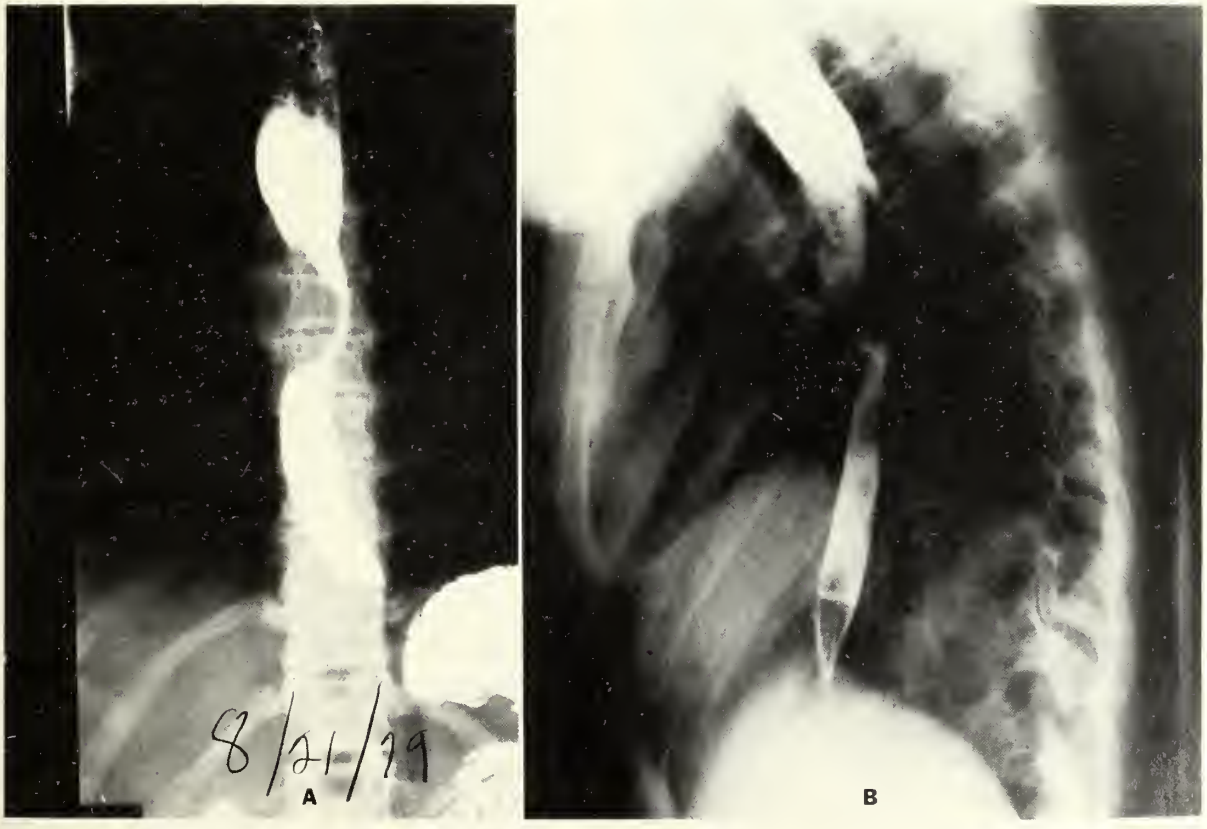


Figure 2.—A & B, Extrinsic compression of the esophagus posteriorly and from the right, as indicated by a fluoroscopic study using orally given barium as the contrast medium.

and sent for pathologieal evaluation. There was no visible communication between the mass lesion and the esophagus or the tracheobronchial tree. Gram stain of the purulent fluid detected Gram-positive filamentous baeteria. From cultured material a delayed growth of *Enterobacter* was noted. The patient was treated with penieillin and her postoperative eourse was uneventful. She was diseharged on August 31. The gross specimen eonsisted of a reddish-brown soft tissue with tan-gray areas. Fungal stains were noncontributory. On mieroseopic evaluation the mass proved to be a eyst lined by ciliated columnar epithelium (Figure 3).

Conclusion

This infeeted bronehogenie eyst did not have the typieal presentation of a visible fistulous tract eommunieating either to the bronehial tree or the esophagus.[11,14] The symptoms in this patient's ease included dysphagia and a fever, with ehest pain, indicative of pleural involvement. The contents of the contaminated eyst initiated a pleural reaetion.

Histologieally, bronchogenie eysts have a lining membrane of eiliated eolumnar epithelium.[18] When infeetion superimposes, however, this lining membrane can be replaeed with granulation tissue, making the diagnosis diffieult. In sueh eases the diagnosis may be based presumptively on the presenee of smooth musele and eartilaginous elements. In this ease, as seen in Figure 3, ciliated eolumnar epithelium was present.

The potential for rupture and a subsequent intrapleural inflammatory reaetion eonstitutes a little-publieized indieation for the surgical exeision of a bronehogenie eyst.

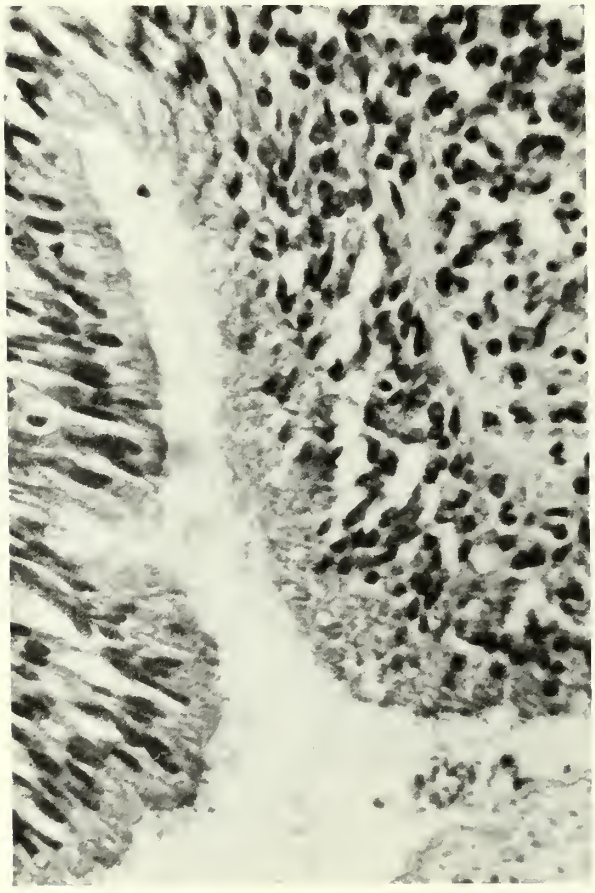


Figure 3.—Cystic component lined by ciliated columnar epithelium (Hematoxylin-eosin stain).

Summary

We report the case of a patient with an infeeted bronehogenic cyst that ruptured into the right pleural cavity, with subsequent fibrinous entrapment of the lung. Assoeiated symptoms of pleurisy and empyema were noted as well.

REFERENCES

1. Morgagni GB: The Seats and Causes of Diseases Investigated by Anatomy. London, Longman, Hurst, Rees, Orme and Brown, 1822

2. Grawitz P: Ueber angeborne bronchiectasie. Virchows Arch Path Anat 82:217-237, 1880

3. Koontz AR: Congenital cysts of the lung. Bull Johns Hopkins Hosp 37:340-361, Nov 1925

4. Bowden KM: Congenital cystic disease of the lung. Med J Aust 2:311-317, Sep 1948

5. Eraklis AJ, Griscom NT, McGovern JB: Bronchogenic cysts of the mediastinum in infancy. N Engl J Med 281:1150-1155, Nov 1969

6. Maier HC: Bronchogenic cysts of the mediastinum. Ann Surg 127:476-502, Mar 1948

7. Alford JE: Congenital bronchogenic cysts of the mediastinum. J Pediatr 11:550-555, Oct 1937

8. Robbins LL: The roentgenologic appearance of "bronchogenic" cysts. Am J Roentgenol Radium Ther Nucl Med 50:321-333, Sep 1943

9. Adams WE, Thornton TF: Bronchogenic cysts of the mediastinum. J Thorac Surg 12:503-516, Aug 1943

10. Collis JL, Clarke DB, Smith RA: D'Abreu's Practice of Cardiothoracic Surgery. London, Butler and Tanner Ltd, 1976, pp 269-271

11. Glenn WW, Liebow AA, Lindskog GE: Thoracic and Cardiovascular Surgery. New York, Appleton Century-Crofts, 1975, pp 434-438

12. Heitzman RE: The Mediastinum. Saint Louis, C.V. Mosby Co, 1977, pp 298-299

13. Reed JC, Sobonya RE: Morphologic analysis of foregut cysts in the thorax. Am J Roentgenol Radium Ther Nucl Med 120:851-860, Apr 1974

14. Blades BB: Surgical Diseases of the Chest. Saint Louis. C.V. Mosby Co, 1966, pp 269-270

15. Moersch HJ, Clagett OT: Pulmonary cysts. J Thorac Surg 16:179-199, Apr 1947

16. Greenfield LJ, Howe JS: Bronchial adenoma within the wall of a bronchogenic cyst. J Thorac Cardiovasc Surg 49:398-404, Mar 1965

17. Leagus CJ, Gregorski RF, Crittenden JJ, et al: Giant intrapericardial bronchogenic cyst. J Thorac Cardiovasc Surg 52:581-587, Oct 1966

18. Schlumberger HG: Tumors of the mediastinum, fasc. 18, Atlas of Tumor Pathology. Washington DC, Armed Forces Institute of Pathology, 1951

Refer to: McCrady-Kahn VL, Kahn AM: Lightning burns. West J Med 134:215-219, Mar 1981

Lightning Burns

VIRGINIA L. McCRADY-KAHN, RN, BSN
ARTHUR M. KAHN, MD
Culver City, California

Our environment presents numerous sources for burn injuries from electricity, chemicals and flammable synthetic materials. Often overlooked are the natural rather than man-made environmental factors such as sun, lightning, lava from erupting volcanoes, and steam and hot water from erupting geysers that can likewise cause burns. The average annual number of deaths in the United States due to lightning accidents is estimated to be between 100 and 600, and lightning causes more deaths directly than does any other weather phenomenon. Surprisingly, about two thirds of those persons involved in lightning accidents make a complete recovery. Most survivors are not directly struck by the lightning but receive electrical shock as a result of being in the close vicinity of a lightning strike.[1] Few physicians see cases of lightning injury, consequently most physicians are inexperienced in the management of these injuries. The purpose of this paper is to present a case of lightning injury and a discussion of the management of such injuries.

Report of a Case

A 10-year-old boy was playing beneath a tree during a rain storm. A bolt of lightning directly struck the tree and the scatter struck the child. Rescuers, almost immediately at the scene, found him to be unconscious, apneic and with his jacket on fire. The fire was extinguished, immediate mouth to mouth respiratory resuscitation was begun and the boy was transported by the paramedic rescue squad to a nearby hospital's emergency room. In the emergency room he vomited then aspirated and was intubated. Following intubation, pulmonary lavage was carried out and administration of corticosteroids was begun. Seizures were observed but not initially treated with anticonvulsant medications. Intravenous fluid therapy was begun and the boy was then transferred by helicopter to our burn center.

Upon arrival at the burn center he was found to be responsive to pain and moving his extremities. Burn wounds were present over 31 percent of his body surface. Typical deep partial and full thickness flame burns were present on both hands, anterior chest, neck, and the right side of the face and scalp. Completely different appearing burns were present on both thighs and the right leg. Over these areas, the burn wounds had a spidery or flower-like appearance (Figure 1).

Immediate and serial radiographic, electrocardiographic and laboratory studies were done. The first x-ray film of the chest showed mediastinal emphysema and this steadily expanded to include the subcutaneous tissue and the subdiaphragmatic intraperitoneal space by the third day. Pulmonary parenchymal infiltrates were present and gradually resolved.

The initial electrocardiogram showed ST segment elevation in leads V_2 and V_3 and this resolved within a few hours. Daily studies of creatine phosphokinase with isoenzymes were done beginning on the day of admission and the cardiac isoenzyme (MB) was never elevated.

Over the course of 12 days the patient's neurological state rapidly improved. Intermittently early seizures were controlled with anticonvulsants. X-ray studies of the skull and computed tomography of the head showed no abnormalities. Electroencephalograms on two occasions were abnormal with an excess of symmetrical slowing. An echoencephalogram was normal.

Upper gastrointestinal bleeding was present; however, it never became massive and was satisfactorily controlled by the hourly instillation of antacids through a nasogastric tube.

Hypertension was noted a few days after admission to hospital. Systolic pressures as high as 180 mm of mercury were observed. Diastolic pressures ranged as high as 110 mm of mercury. The hypertension was poorly controlled by administration of a combination of hydralazine hydrochloride and propranolol hydrochloride. An intravenous pyelogram suggested better concentration of contrast in the right kidney than in the left. An abdominal aortogram showed normal renal arteries and kidneys as did the radiorenogram. Urine catecholamines were not elevated.

From the Burn Center, Brotman Medical Center, Culver City, California.

Submitted March 17, 1980.

Reprint requests to: Arthur M. Kahn, MD, 239 S. La Cienega Blvd., Suite 210, Beverly Hills, CA 90211.

Figure 1.—These two photographs show examples of the typical flower-like appearance of lightning burns.

Administration of the antihypertensive drugs was continued and blood pressure was 112/80 mm of mercury at the time of discharge from the hospital.

The lightning burns on the thighs spontaneously healed, as did most of the areas on the right leg. This healing was complete within ten days. A few areas of full thickness burn were present on the right leg. Multiple operative procedures were required for the treatment of the full thickness burns on the chest, hands, neck and right leg. Split thickness skin grafting of these areas was done.

Intensive occupational, physical and speech therapy was given during the course of the hospital stay and more intensively before the child's discharge 2½ months following his injury. On visits to the office after discharge, the patient was found to have a total mental, physical and emotional recovery.

Discussion

Victims of lightning stroke have disruption of many of their organ systems. The initial response to lightning stroke is paralysis of the vital centers, specifically the respiratory center, resulting in apnea, ventricular fibrillation or cardiac arrest. Artificial resuscitative measures should be begun promptly and continued until there is restoration of vital functions. In the case of our patient it was reported that mouth to mouth resuscitation was begun promptly by a neighbor, a physician, and continued by paramedical personnel at the scene. Upon arrival to a local hospital emergency department, the patient had resumed spontaneous respirations. He then vomited, aspirated and was intubated and placed on a volume ventilator. Numerous cases recounted in the literature give detailed reports of victims suffering respiratory, cardiac or cardiopulmonary arrest as a result of the lightning strike.[2-6] All references emphasized the importance of attempting resuscitation on all lightning stroke victims.[2-6] In fact, some authors have reported the cases of victims found and thought to be dead as a result of lightning stroke who were successfully resuscitated without significant residual damage although they had been without respirations for prolonged or unknown periods of time following injury.[7,8]

Cardiac arrhythmias are commonly seen following lightning injury.[2,5-7] ST segment elevation, T wave inversion and atrial and ventricular arrhythmias have been observed during the acute phase of the injury.[2,6,8,9] Our patient's initial electrocardiogram showed ST segment elevation in leads V_2 and V_3 as well as sinus tachycardia. Subsequent electrocardiograms, within 24 hours after injury, showed resolution of the ST segment elevation. As with our patient, most electrocardiographic abnormalities revert to a normal pattern without myocardial injury. It has been noted that "although minor ECG changes are frequent in survivors of lightning injury, clinical evidence of myocardial damage is uncommon."[6] There have been reports of ventricular fibrillation occurring as a result of lightning injuries. In the past 16 years, there have been only eight cases of documented myocardial injury secondary to lightning.[6] Hypertension has been reported in several cases.[8,9] One author suggested that "transient hypertension and tachycardia are secondary to adrenal stimulation with excess catecholamine release."[6] Hypertension was observed in our patient several days after admission with systolic pressures as high as 180 and diastolic pressures as high as 110 mm of mercury. Administration of hydralazine hydrochloride and propranolol hydrochloride poorly controlled his hypertension which persisted throughout his hospital course. A careful search for the cause of our patient's hypertension was made. What was probably erroneously thought to be a subtle abnormality of the intravenous pyelogram raised the suspicion of a renal vascular cause. However, results of additional studies, which included angiography and renal vein sampling for renin, were all within normal limits. Likewise, urinary catecholamines were not found to be elevated. Even though there is mention in the literature of transient hypertension associated with lightning injury, our patient's hypertension may be related solely to the idiopathic hypertension found in children with thermal injuries rather than any particular relationship to the lightning injury in this case.[10] At discharge our patient's blood pressure was 112 to 120/80 mm of mercury and no further hypertension was noted in follow-up.

Consistent findings of coma, semiconsciousness, amnesia, restlessness, hysteria and keraunoparalysis have been described in the literature.[2-5,7-9] Our patient was reportedly unconscious at the scene but upon admission to our burn facility he was in a semicomatose, restless state, moving all extremities. His level of consciousness vacillated between coma and semicoma, and on the

12th hospital day he was completely awake and out of coma. Seizure activity, another frequently reported response to lightning injury, was observed in our patient on the day of injury and again six days later. At that time, anticonvulsant drug therapy was initiated and no subsequent seizures were observed.

Gastrointestinal complications associated with lightning injuries are not unique but similar to those seen with any type of major trauma or burn injury. The most common problem is early gastroatonia with gastric dilatation. If this is not recognized immediately, vomiting may result and thus there is the ever present threat of aspiration pneumonitis. This avoidable complication occurred in our patient within one hour after injury. Another gastrointestinal problem seen in burn victims, as well as other victims of major trauma, is that of Curling ulcer. Our patient did not have life-threatening upper intestinal bleeding; however, he did have documented gastric bleeding which abated with the hourly administration of antacids through the indwelling nasogastric tube.

Lightning burns, keraunographic markings, spidery arborescent patterns and lightning prints are all terms frequently used to describe the appearance of burn to the skin from lightning. These burns are superficial and heal spontaneously without scarring. In fact, some reports document a disappearance of the keraunographic markings within hours or days following injury. Our patient was admitted with burns over 31 percent of his total body surface area. Burns on his right leg and both thighs were the classic lightning burns or keraunographic markings (Figure 1). Burns on the neck, face, head, chest and right hand were partial and full thickness thermal burns resulting from the lightning igniting the child's jacket. Contemporary burn management, including fluid resuscitation, hydrotherapy and administration of silver sulfadiazine with dressings to the wounds, was implemented. The *lightning burns* were healed by the tenth day after injury. The remaining thermal burns were closed with split thickness autogenous skin grafts.

During the convalescent phase of his care, unsteady gait, problems with coordination while feeding himself and hesitant nasal speech were observed. The boy had intensive physical, occupational and speech therapy while in hospital and was discharged following resolution of these problems. No continuing problems have been observed in this case.

Summary

Lightning injuries, although relatively uncommon, present problems which are not necessarily unique. We wish to stress that respiratory or cardiopulmonary arrest is the most immediate life-threatening complication. Cardiopulmonary resuscitation should be attempted on all lightning stroke victims, should be initiated promptly and should continue until there is a restoration of vital functions.

REFERENCES

1. Uman MA: Understanding Lightning. Carnegie Bek Technical Publications, 1971

2. Apfelberg DB, Masters FW, Robinson DW: Pathophysiology and treatment of lightning injuries. J Trauma 14:453-460, 1974

3. Bennett IL: Harrison's Principles of Internal Medicine. New York, McGraw Hill Book Company, pp 720-721

4. Meyers GJ, Colgan MT, Van Dyke DH: Lightning-strike disaster among children. JAMA 238:1045-1046, 1977

5. Strasser EJ, Davis RM, Menchey MJ: Lightning injuries. J Trauma 17:315-319, 1977

6. Kleines JP, Wilkin JH: Cardiac effects of lightning stroke. JAMA 240:2757-2759, 1978

7. Ravitch MM, Lane R, Safar P, et al: Lightning stroke. N Engl J Med 264:36-38, 1961

8. Taussig HB: "Death" from lightning and the possibility of living again. Ann Intern Med 68:1345-1353, 1968

9. Hanson GC, McIlwraith GR: Lightning injury: Two cases and a review of management. Br Med J 3:271-274, 1973

10. Kravitz M, Baxter CR, Browne R: Hypertension in burned children. Ninth Annual Meeting, American Burn Association, Anaheim, 1977

Refer to: Vyas K, Krishnamurthy GT: Unilateral hydrothorax secondary to ascites—Demonstration by a noninvasive radionuclide imaging technique. West J Med 134:220-222, Mar 1981

Unilateral Hydrothorax Secondary to Ascites

Demonstration by a Noninvasive Radionuclide Imaging Technique

KOKILA VYAS, MD
GERBAIL T. KRISHNAMURTHY, MD
Portland

MANY DIAGNOSTIC TESTS have been used in the past to document the migration of ascitic fluid into the pleural space, manifesting hydrothorax. These include injection of india ink,[1] or Evans blue,[2,3] induction of pneumoperitoneum or injection of albumin labeled with iodine 131 into the peritoneal cavity.[1] Some of these diagnostic tests are either invasive, with some risk,[2,3] or time consuming.[4] Recently, we saw a patient in whom the cause of massive hydrothorax in the absence of any intrathoracic pathologic condition was established within an hour by a noninvasive radionuclide imaging technique. We wish to report this case.

Report of a Case

A 40-year-old man was admitted to hospital for assessment of alcoholic liver disease, ascites and persistent right-sided pleural effusion. Cirrhosis of the liver had been detected several months earlier and pleural effusion and ascites had developed a month before the patient's admission. Findings on physical examination at admission were remarkable by stony dullness with absent breath sounds over the entire right hemithorax. The patient had a large, firm, nontender liver, ascites and edema of both feet. The rest of the physical examination findings were unremarkable. An x-ray study of the chest showed a massive right pleural effusion (Figure 1). Blood gas determinations were normal and liver function tests suggested chronic parenchymal liver disease (albumin 2.29 grams per dl). Multiple investigations, including electrocardiography, thoracocentesis, pleural biopsy, bronchoscopy and other laboratory tests, failed to disclose any intrathoracic cause for pleural effusion. Therefore, the possibility of migration of ascitic transudate into the right hemithorax, manifesting hydrothorax was investigated.

Figure 1.—A roentgenogram of the chest showing a large hydrothorax on the right and clear lung field on the left.

After removal of 3 liters of fluid by thoracocentesis of the right side, 5 mCi of technetium Tc 99m sulfur colloid in 5 ml of saline was injected into the peritoneal cavity in the left lower quadrant under aseptic conditions. After the injection of radioactive colloid, the patient was rolled over a few times and was asked to walk around. The anterior images of the abdomen and thorax with 500,000 counts were obtained, using a large field of view gamma camera (Searle) fitted with parallel hole collimator, immediately after the injection and at ten minutes, one hour, two hours and three hours. At ten minutes, all radioactivity was noted below the right hemidiaphragm and none below the left. At one, two and three hours increasing concentration of radioactivity was noted in the right hemithorax (Figure 2). Migration of technetium Tc 99m sulfur colloid along with ascitic

From the Nuclear Medicine Service, Veterans Administration Medical Center, and the Departments of Clinical Pathology and Medicine, University of Oregon Health Sciences Center, Portland. Dr. Vyas is now in practice in El Dorado, Arkansas.

Submitted, revised, July 25, 1980.

Reprint requests to: G. T. Krishnamurthy, MD, Nuclear Medicine Service (115), Veterans Administration Medical Center, Portland, OR 97201.

fluid into the right pleural space through a hole in the diaphragm was inferred.

Discussion

The occurrence of hydrothorax due to an intra-abdominal pathologic condition in the absence of any intrathoracic cause has been known for a long time, dating as far back as 1895.[1] Several hypotheses have been suggested to explain this paradox. These include leakage of plasma into the pleural space from a hypertensive azygos vein,[5] passage of ascitic fluid into the thorax through the thoracic duct[6] and a structural defect in the diaphragm.[3] Evidence accumulated by injection of albumin labeled with iodine 131 into the ascitic fluid argues against either the thoracic duct lymphatic path or the azygos vein as the usual route of transfer of ascitic fluid into the pleural space.[4]

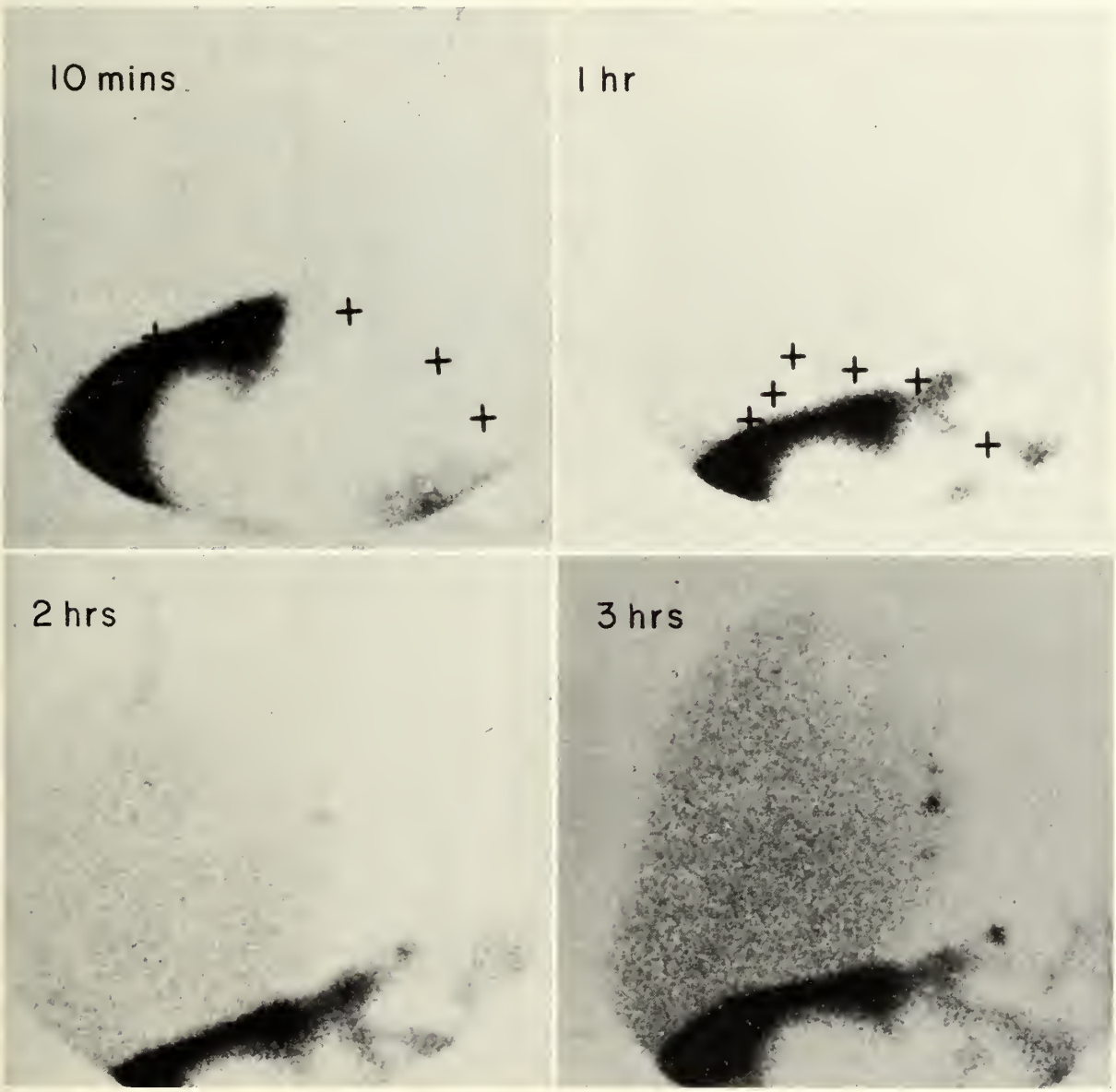


Figure 2.—The anterior images of the abdomen and chest were obtained at ten minutes and one, two and three hours after injection of 5 mCi of technetium Tc 99m sulfur colloid into the left lower quadrant of the abdomen. The image at ten minutes shows radioactivity below the right hemidiaphragm. There is increasing radioactivity in the right hemithorax at one, two and three hours, suggesting the migration of ascitic fluid into the pleural space. Note the absence of any radioactivity below the left hemidiaphragm, indicating the preferential migration of fluid to the right. +'s indicate costal margin.

Evidence accumulated by thoracoscopy, postmortem findings and induction of pneumoperitonium strongly suggests diaphragmatic defects as the most common cause of hydrothorax.[2,4,7] The size of the defect in the diaphragm may vary anywhere from 1 mm to several centimeters, allowing the free flow of fluid from the abdomen into the pleural space.[2,4] Interestingly, in our patient all the radioactivity migrated preferentially under the right hemidiaphragm despite the fact that the fluid was injected into the left lower quadrant, indicating the direction of the flow of fluid (Figure 2). Usually, negative intrathoracic pressure facilitates rapid flow of fluid from the abdomen. In one reported case of a patient with ascites resulting from cirrhosis of the liver, thoracocentesis was done 211 times during 14 months, with removal of 467,000 ml of fluid that was grossly identical to the ascitic fluid.[8] The diaphragmatic defects are more common on the right side than on the left. In a study of 21 patients reported by Lieberman and Peters, a right-sided defect was found in 15 patients.[9]

The radionuclide imaging technique described above is noninvasive and provides information within a short time. Many of the previous tests were either complicated or took 24 to 72 hours to yield adequate information.[1-4] The induction of pneumoperitoneum requires the patient to be seated for 24 hours. It is anticipated that the current technique may serve as an alternative to many of the previous invasive and nonphysiological diagnostic tests.

Summary

In a patient with hepatic cirrhosis and recurrent right-sided hydrothorax, rapid migration of ascitic fluid into the right pleural cavity was detected by a noninvasive radionuclide imaging technique. Technetium Tc 99m sulfur colloid particles injected into the peritoneal space entered the right pleural cavity within an hour. A congenital defect in the right hemidiaphragm appears to be the likely route of fluid transfer.

REFERENCES

1. Meigs JV, Armstrong SH, Hamilton HH: A further contribution for the syndrome of fibroma of ovary with fluid in the abdomen and chest-Meigs syndrome. Am J Obstet Gynecol 46: 19-37, 1943

2. Emerson OA, Davies JH: Complicating ascites. Lancet 268 (1):487-488, 1955

3. Williams MH: Pleural effusion produced by abdominopleural communication in a patient with Laennec's cirrhosis of the liver. Ann Intern Med 33:216-221, 1950

4. Lieberman FL, Hidemma R, Peters RL, et al: Pathogenesis and treatment of hydrothorax complicating cirrhosis with ascites. Ann Intern Med 64:341-351, 1966

5. Morrow CS, Kantor M, Armen RN: Hepatic hydrothorax. Ann Intern Med 49:193-203, 1958

6. Eisenmenger WJ: Edema associated with liver disease in edema: Its mechanism and management, *In* Moyer JH, Fuch MW (Eds): A Hahneman Symposium on Salt and Water Retention. Philadelphia, Saunders Co, 1960, p 626

7. Singer JA, Kaplan MM, Katz RL: Cirrhotic pleural effusion in the absence of ascites. Gastroenterology 73:575-577, 1977

8. Frothingham JR: Cirrhosis of the liver complicated by persistent right hemithorax and ascites. N Engl J Med 226:679-681, 1942

9. Lieberman FL, Peters RL: Cirrhotic hydrothorax—Further evidence that an acquired diaphragmatic defect is at fault. Arch Intern Med 125:114-117, 1970

Refer to: Sack RL, Shore JH: Psychopharmacology in medical practice—The benefits and the risks (Medical Progress). West J Med 134:223-233, Mar 1981

Psychopharmacology in Medical Practice—The Benefits and the Risks

ROBERT L. SACK, MD, *and* JAMES H. SHORE, MD, *Portland*

Psychopharmacology has become a major approach to treatment in primary medical care. However, combined psychiatric and medical illness can give rise to some challenging diagnostic problems. Furthermore, drug treatment of patients with such illnesses can involve important drug-disease interactions and drug-drug interactions. One should keep in mind the issues that arise when an emotionally troubled patient would benefit from a psychotropic drug but a concurrent medical illness complicates this treatment. An awareness of both the medical and psychiatric issues involved may make successful treatment possible.

PSYCHOPHARMACOLOGY HAS BECOME a major part of medical practice.[1-3] A survey by Parry and associates showed that 22 percent of the population had used a prescription psychotropic drug in the preceding year and that most of these drugs were prescribed by nonpsychiatric physicians.[4] Diazepam is still the most frequently prescribed drug in the world. Tricyclic antidepressants are increasingly prescribed by nonpsychiatric physicians, as well as by psychiatrists.

In recent years concern has been raised about this heavy use of psychopharmacology, some critics alleging that we are becoming an "overmedicated society."[5] Perhaps in response, the use of benzodiazepines appears to be in decline.[6] A number of studies have been conducted to gauge the extent of possible misuse of prescription psychotropic drugs and have concluded that, while individual instances of abuse are certainly a problem, most patients use prescription psychotropic drugs appropriately and are appreciative of the benefits derived.[7-9]

From the Department of Psychiatry, University of Oregon Health Sciences Center, Portland.

Reprint requests to: Robert L. Sack, MD, Dept. of Psychiatry, University of Oregon Health Sciences Center, Portland, OR 97201.

Why are psychopharmacologic treatments so popular with general physicians? Studies of primary care practices indicate that a sizable number of patients complain to their physicians of mental and emotional difficulties. Indeed, it appears that more people seek help for these problems from their primary physicians than from special mental health clinics.[10] Psychotropic drugs have proved effective for many common emotional illnesses. The use of psychopharmacology fits more naturally into a medical practice than other psychiatric treatments such as formal psychotherapy.

Other reasons for the heavy use of psychopharmacology may not be easily justifiable. Physicians may reach for a prescription pad rather than hear out the concerns of a troubled patient. They may use drugs to modify symptoms when more fundamental changes are needed.

Another criticism of the use of psychopharmacologic drugs is that they are prescribed by many physicians who do not seem to devote the kind of attention to the indications, dosage schedules and side effects as they would with other drugs. For example, one study showed that most patients treated for depression with a tricyclic antidepres-

sant were receiving an inadequate dose for an extended period of time even though their symptoms were not responding.[11] New developments in the standardization of psychiatric diagnosis and in the understanding of pharmacokinetics of psychopharmacologic drugs now make the use of these drugs more rational and less empirical than was once the case.

In this paper we will address the issue of appropriate use of psychopharmacology in the *medical context.* As for any class of drugs, appropriate use depends on a knowledge of *diagnosis, indications* for drug treatment and potential *risks.* For a medically ill patient, each of these facets of psychopharmacology is more complex because the issues of physical symptoms, diseased organs and drug-drug interactions have to be considered alongside the psychiatric problems under treatment.

Diagnosis and Indications

The chances of successful drug treatment are increased and the risks of abuse are diminished when a specific psychiatric diagnosis can be made and the most appropriate drug for that syndrome is selected. When psychotropic drugs are used to counteract *symptoms,* the effects are much more unpredictable. A discussion of the differential diagnosis of psychiatric illness is well beyond the scope of this paper; nevertheless, a few points about psychiatric diagnosis in the context of medical illness are important in this discussion.

The task of making a specific and relevant psychiatric diagnosis has been made easier for psychiatrists and nonpsychiatrists alike with the adoption of the *Diagnostic and Statistical Manual —Third Edition,* the DSM-III.[12] This document, which has been a major preoccupation among psychiatrists for the past six years, has now been officially adopted by the American Psychiatric Association. It contains explicit, operationally defined, diagnostic criteria for all psychiatric diagnoses. For an example, see Table 1 which lists the diagnostic criteria for a major depressive episode.

In some cases—for example, depression—the formal diagnostic criteria correlate highly with the factors found to predict successful drug therapy. In other words, the more closely the patient fits the diagnostic criteria, the more likely he will respond to pharmacological treatment.[13] If he lies in the *gray zone,* the probability of successful treatment diminishes. If drug treatment is contemplated, it can be useful to review the diagnostic criteria for the entity to be treated before embarking on a course of therapy. (The DSM-III can be purchased from the American Psychiatric Association.*)

*American Psychiatric Association, Publication Sales, 1700 18th Street, N.W., Washington, DC 20009. Price: $20.00 paperback; $25.00 casebound.

TABLE 1.—*Diagnostic Criteria for Major Depressive Episode**

A. Dysphoric mood or loss of interest or pleasure in all or almost all usual activities and pastimes. The dysphoric mood is characterized by symptoms such as the following: depressed, sad, blue, hopeless, low, down in the dumps, irritable. The mood disturbance must be prominent and relatively persistent, but not necessarily the most dominant symptom, and does not include momentary shifts from one dysphoric mood to another dysphoric mood, e.g., anxiety to depression to anger, such as are seen in states of acute psychotic turmoil. (For children under six, dysphoric mood may have to be inferred from a persistently sad facial expression.)

B. At least four of the following symptoms have each been present nearly every day for a period of at least two weeks (in children under six, at least three of the first four):
   (1) poor appetite or significant weight loss (when not dieting) or increased appetite or significant weight gain (in children under six, consider failure to make expected weight gains);
   (2) insomnia or hypersomnia;
   (3) psychomotor agitation or retardation (but not merely subjective feelings of restlessness or being slowed down) (in children under six, hypoactivity);
   (4) loss of interest or pleasure in usual activities, or decrease in sexual drive not limited to a period when delusional or hallucinating (in children under six, signs of apathy);
   (5) loss of energy; fatigue;
   (6) feelings of worthlessness, self-reproach, or excessive or inappropriate guilt (either may be delusional);
   (7) complaints or evidence of diminished ability to think or concentrate, such as slowed thinking, or indecisiveness not associated with pronounced loosening of associations or incoherence;
   (8) recurrent thoughts of death, suicidal ideation, wishes to be dead or suicide attempt.

C. Neither of the following dominate the clinical picture when an affective syndrome is absent (i.e., symptoms in critera A and B above):
   (1) preoccupation with a mood-incongruent delusion or hallucination;
   (2) bizarre behavior.

D. Not superimposed on either schizophrenia, schizophreniform disorder or a paranoid disorder.

E. Not due to any organic mental disorder or uncomplicated bereavement.

*Reprinted by permission from Diagnostic and Statistical Manual of Mental Disorders, Third Edition. Washington, DC, The American Psychiatric Association, 1980, pp 213-214.

Patients with significant medical illness who have symptoms that overlap with the symptoms of a psychiatric disorder present a diagnostic challenge. For example, a patient with carcinoma may have anorexia, a sleep disturbance and a sad affect. These symptoms may be explained on the basis of the medical diagnosis or with a diagnosis of depression (Table 1). One helpful strategy in differentiating these possibilities is to look for the remaining elements of a depressive syndrome; for example, difficulty concentrating, guilt, diurnal variation and the like. In some difficult cases there is no choice but to begin a clinical trial of psychotropic medication. It can be a significant error to withhold treatment from a medically ill patient whose psychiatric symptoms may seem "understandable" in the context of his physical illness but who is found to obtain considerable relief with carefully managed drug therapy.

While a good many patients report overt emotional complaints to their primary physicians, a sizable group complain of physical symptoms which, upon investigation, are medically unexplained and are presumed to be psychogenic in origin. These kinds of complaints frequently are reasons for prescribing psychotropic drugs. Anxiety or depression is hypothesized to underlie the complaints. While this rationale may have merit, there is much less evidence to support pharmacological interventions for such indications than for clear-cut psychiatric syndromes.

However, there are a few fairly well-known clinical entities in which a primary psychiatric disorder is masked by somatic complaints. For example, a psychogenic pain syndrome is often associated with depressive features on psychological testing and is frequently responsive to tricyclic antidepressants; thus, a significant number of such cases may be considered "masked depressions."[14] Another example is "depressive pseudodementia," a disorder of older patients in which affective

TABLE 2.—Antianxiety Agents. *Pharmacological Profile of Factors That May Influence Drug Selection in Medically Ill Patients*

Benzodiazepines	*Sedation*	*Elimination Half-Life*[17]	*Intramuscular Absorption*[18]	*Active Number of Metabolites*[17]	*pH Dependent Intragastric Conversion*[19]	*Representative Brands*
Chlordiazepoxide	2	5-30 hrs	Variable	3	0	Librium
Diazepam	3	20-50 hrs	Variable	1	0	Valium
Oxazepam	2	5-20 hrs	Parenteral form not available	0	0	Serax
Clorazepate	3	30-60 hrs	Parenteral form not available	1	+	Tranxene, Azene
Prazepam	2	20-50 hrs	Parenteral form not available	2	+	Verstran
Lorazepam	2	10-15 hrs	Parenteral form not available	0	0	Ativan
Flurazepam	3	47-100 hrs	Parenteral form not available	1	0	Dalmane

When compared to other drugs of the same class:
1—"least" 2—"intermediate or average" 3—"most"

TABLE 3.—Antidepressant Drugs. *Pharmacological Profile of Factors That May Influence Drug Selection in Medically Ill Patients*

	Sedation[20]	*Anticholinergic Activity*[21]	*Slowed Cardiac Conduction*[22-25]	*Postural Hypotension*[26]	*Elimination Half-Life*[27]	*Type of Amine*	*Metabolism*	*Representative Brands*
Tricyclic Antidepressants								
Imipramine	2	2	3	2	8 hrs	3°	↓	Tofranil
Desipramine	1	1	3	1	17 hrs	2°	↓	Norpramin, Pertofrane
Amitriptyline	3	3	2	3	15 hrs	3°	↓	Elavil, Endep
Nortriptyline	1	1	2	2	27 hrs	2°	↓	Aventyl, Pamelor
Protriptyline	0	2	2	1	78 hrs	2°		Vivactil
Doxepin	3	3	1	3	17 hrs	3°	↓	Sinequan, Adapin
Desmethyldoxepin	..	..	..	..	51 hrs	2°	↓	(Not marketed)
Monoamine Oxidase Inhibitors								
Tranylcypromine	0	1	0	1	1-2 wks*	..		Parnate
Phenelzine	0	1	0	1	1-2 wks*	..		Nardil

When compared to other drugs of the same class:
1—"least" 2—"intermediate or average" 3—"most"

*Time needed for monoamine oxidase activity to be restored.

complaints are masked behind major concerns with the loss of cognitive functions.[15]

Because of these and other less easily classified examples of drug-sensitive disorders hiding behind somatic symptomatology, a trial of psychotropic agents is sometimes warranted even when a specific diagnosis cannot be made. However, in such instances, the attitude of the physician should be that of conducting a clinical trial. The goals of treatment should be stated as clearly as possible in the record and to the patient. The dose of the selected drug should be increased to the therapeutic range and sustained for a planned period of time. If no response is observed, the drug should be tapered and discontinued.

The theme of the foregoing discussion has been the importance of basing intervention on the diagnosis of a specific psychiatric entity. This is true especially for the affective disorders. There is little hope of lifting the pain of a realistic tragedy with an antidepressant. Likewise, lithium will not dampen the euphoria that comes with genuine good fortune.

Notwithstanding, some psychopharmacologic drugs *do* counter symptoms as well as syndromes. For example, the antipsychotic drugs are not only useful in schizophrenia (the most frequent indication), but are useful in the acute manic episode and in psychotic depression. In low doses they can be dramatically effective in the agitated, delirious patient. Antianxiety drugs seem to modify "realistic" anxiety as well as neurotic anxiety; for example, they are quite effective in calming patients before operations.

Some psychopharmacologic drugs have a spectrum of action beyond psychiatric symptoms. For example, the phenothiazine drugs are useful antiemetics; benzodiazepines are useful in the treatment of status epilepticus. Occasionally novel effects for psychotropic drugs are reported which may be an extension of their psychotropic properties or may be quite independent. The prophylactic effect of tricyclic antidepressants in migraine syndrome[16] may be by modification of psychological functioning or may be due to some other property of drugs.

Although treating a psychiatric disorder in the context of a physical illness may sometimes be difficult and, on occasion, risky, the benefits can be important not only for the emotional well-being of the patient, but for the recovery from physical illness as well. Untreated psychiatric problems may place added strain on already diseased organs. Furthermore, a patient who is severely anxious, depressed or psychotic will have great difficulty complying with medical treatment. In assessing the ratio of benefit to risk, one has to include the risk to the physical health of the patient by *not* treating a psychiatric illness, as well as the risk to physical health presented by the side effects of psychotropic drugs.

TABLE 4.—Antipsychotic Drugs. *Pharmacological Profile of Factors That May Influence Drug Selection in Medically Ill Patients*

	Sedation[28]	*Extrapyramidal Side Effects*[28]	*Anticholinergic Activity*[29]	*Postural Hypotension*[28]	*Slowed Cardiac Conduction*	*Representative Brands*
Phenothiazines						
Chlorpromazine	3	2	2	3	..	Thorazine
Thioridazine	3	1	3	3	3	Mellaril
Mesoridazine	3	1	3	3	3	Serentil
Prochlorperazine	2	2	2	2	..	Compazine
Perphenazine	2	2	2	2	..	Trilafon
Trifluoperazine	2	2	2	2	..	Stelazine
Fluphenazine	1	3	2	2	..	Prolixin
Thioxanthene						
Thiothixene	2	2	2	2	..	Navane
Butyrophenones						
Haloperidol	1	3	1	1	..	Haldol
Droperidol	1	3	1	1	..	Inapsine
Dibenzoxazepines						
Loxapine	2	2	2	2	..	Loxitane
Indolics						
Molindone	2	2	2	2	..	Moban

When compared to other drugs of the same class:
1—"least" 2—"intermediate or average" 3—"most"

Risks

Because there is a large amount of information to be included under the potential risks of psychopharmacologic drugs from side effects, drug-disease interactions and drug-drug interactions, this material has been summarized in a number of tables. In Tables 2 through 4 the pharmacological characteristics that might affect the choice of drug from within each class are presented. In Table 5 potential drug-disease interactions are listed (excluding the drug-drug interactions that might result from the drugs typically employed for those diseases). In Table 6 significant drug-drug interactions are listed.

Some general categories of medical patients carry common risk factors. For example, as a general rule pregnant women should not receive medications of any kind unless it is considered essential. Studies have suggested that exposure during pregnancy to lithium leads to an increase in the incidence of the Ebstein malformation of the heart in the newborn,[59] and of cleft palate with benzodiazepine use.[60] Guidelines for minimizing risks of psychopharmacologic treatment during pregnancy can be found in the review by Goldberg and DiMascio.[61] Another category, the elderly, metabolize many drugs more slowly and are more sensitive to side effects.[62] It is wise, as a general rule, to reduce the usual dose to half in patients older than 65 years, at least at the initiation of drug treatment.

Antianxiety Agents

Benzodiazepines are the most prescribed psychotropic drugs in medicine today.[2] They are mainly indicated as antianxiety agents, but they are used as muscle relaxants and anticonvulsants as well. Benzodiazepines are typically somewhat sedative, but the reduction in anxiety is independent of their sedative effects. The mechanism of action of the benzodiazepines is unknown, although current evidence suggests that their effects may be mediated through the GABA (gamma aminobutyric acid) system.[63] Recently, a specific "Valium receptor" has been discovered in the brain, suggesting that these drugs may be interacting with an endogenous neuromodulator that has yet to be defined.[64]

Undoubtedly the tremendous popularity of the benzodiazepines as antianxiety agents derives from their remarkable safety, especially when compared with their predecessors, the barbiturates. The main risk for the benzodiazepines is psychological dependence, and to a much lesser degree, physiological dependence. Again, contrasting them with barbiturates, these risks are significantly less.

The benzodiazepines may disinhibit ordinarily suppressed behavior. For example, patients may be more likely to express hostile feelings and may be more apt to lose emotional control.[65] Some patients find benzodiazepines depressogenic.

It appears to be nearly impossible to commit suicide with benzodiazepines alone, although they potentiate the respiratory depression and other toxic effects of sedative agents such as alcohol and barbiturates.

There are some significant differences in the properties of the available benzodiazepines, although the basic efficacy in the treatment of anxiety is similar. For example, chlordiazepoxide has three active metabolites which are formed in the liver. Therefore, the duration of pharmacological activity can be affected by the rate of hepatic metabolism which can be reduced in liver disease. Flurazepam has a very long duration of action which may account for the lack of rebound insomnia when this drug is used as a nighttime sedative.[66] On the other hand, this long half-life may contribute to significant daytime drowsiness. To help a patient get to sleep during an occasional episode of insomnia, one might chose oxazepam which has a short half-life and no active metabolites. Two of the benzodiazepines, clorazepate and prazepam, are transformed in the stomach to active drugs. This process is dependent on the pH of the stomach and can be inhibited by antacid therapy.[19]

Chlordiazepoxide and diazepam are the only benzodiazepines available for parenteral use; however, intramuscular absorption is variable and thus the oral or intravenous route is preferable. Lorazepam seems to be evenly absorbed intramuscularly, but a parenteral form is not yet available in the United States.[67]

Although the propanediols, such as meprobamate, are also very safe in medically ill patients, they are much more likely to cause withdrawal effects and to be lethal if taken in overdose. For these reasons, they are second-order drugs in the treatment of anxiety.

Tricyclic Antidepressants

Tricyclic antidepressants have potent effects on a number of neurotransmitter systems. They block the synaptic reuptake mechanisms for norepi-

TABLE 5.—*Common Drug-Drug Interactions*

	Benzodiazepines	*Tricyclic Antidepressants*	*Phenothiazine Antipsychotics*	*Butyrophenones*	*Lithium*	*MAO Inhibitors*	*Clinical Implications*
Anticholinergics	0	2	2	1	0	1	*Additive Anticholinergic Effects* Additive anticholinergic effects can cause constipation, paralytic ileus, urinary retention, fever, tachycardia and delirium.[30] Dental caries are a secondary effect of dry mouth.[31] Acute anticholinergic toxicity may be reversed with physostigmine.[32,33]
Antacids	1	1	1	1	0	..	*Diminished Absorption* Antacids may diminish the absorption of phenothiazines[34] and benzodiazepines[35]; also, antacids may inhibit the intragastric conversion of some benzodiazepines.[19]
Sedative hypnotics	2	0	0	0	0	0	*Cross-tolerance* All sedative hypnotic drugs, including barbiturates and alcohol, manifest cross-tolerance with benzodiazepines.
	2	2	2	1	1	0	*Additive Sedative Effects* Most psychotropic drugs produce some degree of sedation which will add to the effects of alcohol or other sedatives.[36]
Opiate analgesics	1	1	1	1	0	3	*Potentiation of Analgesic Activity* Psychotropic drugs can potentiate the analgesic action of opiates.[14,37-39] However, the combination of meperidine (Demerol) and MAO inhibitors can be hazardous.[40]
Antihypertensive drugs							*Inhibition*
Guanethidine	0	2	2	0	0	..	Antihypertensive drugs which depend on "amine pump" uptake into the cell are blocked by
Clonidine	0	2	2	0	0	..	2° amine tricyclics and by chlorpromazine.[41]
Sodium-depleting diuretics	0	0	0	0	3	0	*Lithium Toxicity* Sodium-depleting diuretics stimulate the kidney to retain lithium.[42,43]
Beta-blockers	0	1	1	0	0	..	*Inhibition* Tricyclics and phenothiazines can diminish the effectiveness of beta-blockers.[26]
Pressor amines	0	0	0	0	0	3	*Acute Hypertensive Crisis* Pressor amines, as well as foods containing tyramine, can precipitate an acute hypertensive crisis in patients taking an MAO inhibitor.[44]
Antihistamines							
H_1-blockers	1	1	1	1	1	..	*Additive Sedative Effects* Most psychotropic drugs have some sedative effects.[45]
H_2-blockers	1	1	1	..	..	..	*Mixed* Cimetidine can impair the elimination of benzodiazepines.[46] Tricyclics and phenothiazines have H_2 receptor blocking effects[45] which are probably additive with cimetidine.
Quinidine	0	2	2	..	..	..	*Cardiac Arrhythmias* Additive slowing of cardiac conduction may lead to arrhythmias.[42]

0—No interaction 1—Known interaction but clinical importance variable 2—Interaction usually significant 3—Hazardous interaction
MAO = monoamine oxidase

TABLE 6.—*Drug-Disease Interactions**

	Benzo-diazepines	*Tricyclic Antide-pressants*	*Pheno-thiazine Anti-psychotics*	*Butyro-phenones*	*Lithium*	*MAO Inhibitors*	*Clinical Implications*
Hypertension	T	..	..	..	..	T	Benzodiazepines are reported to be beneficial in mild hypertension.[47] Pargyline (Eutonyl), a MAO inhibitor, is marketed as an antihypertensive.[48]
Cardiac disease							
Arrhythmias	S	T,H	T,H	S	..	..	The quinidine-like effects of tricyclic antidepressants and some phenothiazines (especially thioridazine) may be hazardous in the patient with conduction defects,[22] but beneficial for myocardial irritability.[23,24]
Congestive failure	S	H	H	..	..	..	Tricyclic antidepressants and phenothiazines have been reported to worsen congestive failure.[25]
Coronary vascular	T?,S	H	H	S	..	..	Postural hypotension may reduce coronary perfusion. Benzodiazepines are useful in acute postmyocardial infarction treatment.[49]
Liver disease	H	H	H	H	S	H	Since all psychotropic drugs (except lithium) are partially metabolized in the liver, toxic levels can accumulate in severe liver disease.[50,51]
Kidney disease	H	H	H	H	C	H	Since lithium is excreted entirely by the kidney, it should not be given in renal failure. Other drugs can be given if monitored closely.[52]
Gastrointestinal							
Irritable bowel and "functional" complaints	T	S	S	S	S	S	Tricyclic antidepressants have recently been shown to have strong H_2 receptor blocking activity[44] which may explain the therapeutic effect in peptic ulcer disease.[53]
Peptic ulcer	T	T	S	S	S	S	Antianxiety agents are popular treatments for a variety of gastrointestinal conditions.[54]
Dermatological disease	T	T	T	T	..	..	Psychotherapeutic drugs may help in stress-related eruptions.[55]
Respiratory disease							
Respiratory insufficiency	H	H	H	H	H	..	Most psychotherapeutic drugs have at least some respiratory depressant effects.
Asthma	T	T	T	..	..	..	Psychotropic drugs have been reported to be useful adjuncts.[56]
Neurological							
Cerebral vascular disease	S	H	H	S	..	H	The main risk is postural hypotension leading to inadequate perfusion and stroke.
Migraine	..	T	..	..	..	..	Amitriptyline recently reported as effective prophylaxis in migraine.[16]
Delirium and dementia	H	T,H	T,H	T,H	..	..	Phenothiazines and butryophenones can be quite helpful in organic brain syndromes if used in small doses. If overused, they can intensify confusion.
Chronic pain syndromes	S	T	T	T	..	..	For reviews, see Table 3, references 24-27.
Hematologic							
Leukopenia	..	..	..	..	T?	..	Lithium stimulates leukocyte production.[57]
Pregnancy	H	H	H	H	H	H	All drugs should be considered hazardous.

T—Potentially therapeutic S—Reported as safe H—Potentially hazardous C—Contraindicated

*Excluding potential drug-drug interactions for drugs typically used in these conditions.

nephrine and serotonin. They are strongly anticholinergic (antimuscarinic) and antihistaminic. The reuptake blockade has been invoked to explain their therapeutic effects since it fits the catecholamine theory of depression;[68] however, there are many reasons to doubt that this action is a sufficient explanation for their antidepressant effects.[69]

The tricyclics can be subdivided chemically into the tertiary and secondary amine categories (See Table 3). The tertiary amines are more active with the serotonin reuptake system while the secondary amines differentially affect the noradrenergic system. It has been suggested that this difference may be important in subcategorizing depressions as *serotonergic* and *noradrenergic* depending on which class of tricyclics is effective.[70] Failure to respond to a secondary amine tricyclic might, at least, prompt a trial with a tertiary, and vice versa. However, since the tertiary drugs are metabolized to secondary tricyclics, this differential neurotransmitter effect is not completely specific.

The risks for a medical patient taking tricyclic antidepressants begin with their autonomic side effects. Anticholinergic manifestations include dry mouth, blurred vision and urinary retention. The postural hypotension typical of these drugs is most likely secondary to alpha-adrenergic blockade. These side effects are mainly a nuisance for healthy patients, but can be very serious for those who are medically ill. For example, postural hypotension may precipitate a vascular accident in a patient with transient ischemic episodes. A syncopal fall in an elderly patient may result in a broken hip with complications. Since there is considerable variation in autonomic side effects among the various available compounds, it is wise to consider the autonomic profile when choosing a drug. Table 3 lists some of the characteristics of tricyclic antidepressants that might influence the choice of a drug, especially in medically ill patients.

Perhaps the most worrisome side effect from the tricyclics is their alleged cardiotoxicity. Considerable controversy has developed in this matter. There is no question that an overdose of tricyclics can lead to arrhythmias, but the danger of these drugs in the usual doses is still debated. One source of risk derives from the effects of these drugs on electrical conduction of the heart. By and large, tricyclics act like quinidine, slowing the conduction time. Such an effect might be safe, indeed therapeutic, in a patient with increased myocardial irritability. On the other hand, for a patient with conduction defects this could lead to complications. Doxepin appears to have the least effect on cardiac conduction and is the drug of choice when this factor is a major consideration.

The monoamine oxidase inhibitors are rarely used in this country. Most physicians in the United States abandoned them after reports of hepatic toxicity (now known to be rare), and the famous "cheese reaction." However, their use was sustained in Great Britain, and problems have been rare. The monoamine oxidase inhibitors may be undergoing a comeback in this country.

Several new classes of antidepressants are under development.[71-76] Clinical trials have shown efficacy which compares favorably with the tricyclics; furthermore, they appear to be safer in many respects. Some of these newer antidepressants may be especially useful for medically ill depressed patients when (and if) the drugs become available in the United States.

Antipsychotics

Antipsychotic activity is closely related to dopaminergic receptor blockade. However, antipsychotic drugs may have anticholinergic (antimuscarinic), antihistaminic and adrenergic blocking effects as well.

The phenothiazine derivatives (chlorpromazine, thioridazine and the like) all produce postural hypotension to some degree. Therefore, when an antipsychotic drug is required in a medically ill patient, haloperidol is frequently preferred. Some antipsychotic drugs, such as thioridazine, have quinidine-like effects similar to the tricyclics and thus must be used with caution in patients with a preexisting conduction defect.

A long-term risk in using the antipsychotic compounds is the occurrence of tardive dyskinesia. For this reason, these compounds should not be employed when other approaches are available; for example, they should not be employed as antianxiety agents as has been sometimes advocated in the past.

Clinical Examples

In the last section of this paper, some examples will be provided of the ways in which thoughtful consideration of the various aspects of psychopharmacological treatment advanced the care of some difficult clinical problems in a general hospital.

CASE 1. A 45-year-old man who had never been in the hospital in his life was admitted with a large myocardial infarction. On the third hospital day he became acutely paranoid, believing that his wife had been unfaithful while he was confined to the hospital. He demanded discharge against advice and was poised to do combat with anyone who challenged him. His cardiac status was quite marginal and there was serious concern that he would not survive if he left the coronary care unit. After a court hold was signed, a dose of droperidol, 5 mg, was administered intravenously. Within a few minutes he was calm and manageable. This was followed by the use of small doses of haloperidol over the next few days. The day after this incident, he apologized to the staff and said he "didn't know what came over him."

Comment. This patient was probably suffering from a mild delirium from the use of sedative agents given routinely to myocardial infarction patients. In addition, the sleep deprivation and unfamiliarity of the coronary care unit environment contributed to his loss of control. By the time he exploded, verbal reassurance was ineffectual and pharmacological intervention was required. Further sedation would have most likely intensified his delirium; therefore, a relatively nonsedating antipsychotic drug was used. Because of his recent myocardial infarction and the need to avoid any hypotensive side effects, a drug from the butyrophenone group was selected. Finally, because of the need for fast intervention, droperidol was selected because of the advantage of intravenous administration.

CASE 2. A 51-year-old police investigator presented with depression and suicidal ideation made more compelling because of his easy access to firearms. Five years before, an operation had been done for extensive coronary vascular disease in which three vessels were bypassed. He had done quite well since the operation except for chronic painful dysesthesias around the site of his sternotomy scar. In collaboration with his cardiologist who obtained serial electrocardiograms, he was treated with doxepin with good results. He noticed that the dysesthesias were greatly diminished with tricyclic therapy.

Comment. Doxepin seemed to be a rational choice in this patient because of its minimal effects on cardiac conduction, although postural hypotension could have been a problem. A bonus from this treatment was the relief from the chronic pain syndrome; this is an effect of tricyclics that may be independent of the antidepressant effect.

CASE 3. A 65-year-old man was moderately demented from a slow-growing astrocytoma which was inoperable. He was irritable, distractable and emotionally labile. Haloperidol, 1 mg twice a day, helped him to focus his thoughts more clearly and to be more sociable with the other patients and with the staff.

Comment. Low doses of antipsychotic drugs can be remarkably effective in helping a mildly demented patient order his or her thoughts more effectively. A common error is to sedate such patients heavily, adding to their confusion.

CASE 4. A 26-year-old woman, a graduate student, had been seen by many doctors for somatic complaints. She suffered periods of shortness of breath, an impending sense of doom, and cardiac palpitations which were both incapacitating and mysterious. After some extensive interviewing, she defined her problem more explicitly as anticipatory anxiety about going to a classroom. She suffered very unrealistic fears that she would lose control in such a setting and humiliate herself. She was prescribed diazepam to take before she went to class. It was highly successful in limiting her symptoms and her somatic complaining ceased.

Comment. Benzodiazepines can be very helpful in cases of panic disorder. This case illustrates how judicious use of the drug minimizes dependence and unwanted side effects. Somatic preoccupation appeared to be secondary to her need to find an explanation for her panic attacks.

CASE 5. A 32-year-old man with a history of Crohn disease was under treatment for a recurrent psychosis. Because of symptoms of depression, a tricyclic antidepressant was added. Over the next week nausea and vomiting developed which he attributed to the "flu." However, when he was examined several days later, he was found to be grossly distended and without bowel sounds. He was admitted to hospital where administration of medications was stopped and he was treated with decompression and intravenously given fluids. He recovered without any need for surgical therapy. He was subsequently treated successfully with an antipsychotic drug with low anticholinergic activity.

Comment. This man probably had a paralytic ileus from the combined anticholinergic side effects of a tricyclic antidepressant and a phenothiazine antipsychotic. Previous surgical procedures

for Crohn disease may have left him with adhesions that contributed to the problem.

Conclusions

Psychopharmacology has become an important part of overall medical care. Given the important role psychotropic drugs play in medical practice, knowledge of their indications, actions and hazards should rank alongside that required for the skillful use of other potent drugs.

REFERENCES

1. Greenblatt D, Shader R, Koch-Weser J: Psychotropic drug use in Boston area: A report from Boston Collaborative Drug Surveillance Program. Arch Gen Psychiatry 32:518-521, 1975

2. Blackwell B: Psychotropic drugs in use today: The role of diazepam in medical practice. JAMA 225:1637-1641, 1973

3. Gottschalk LA, Bates DE, Fox RA, et al: Psychoactive drug use: Patterns found in samples from a mental health clinic and a general medical clinic. Arch Gen Psychiatry 25:395-397, 1971

4. Parry HJ, Balter MB, Mellinger GD, et al: National patterns of psychotherapeutic drug use. Arch Gen Psychiatry 28:769-783, 1973

5. Muller C: The over-medicated society: Forces in the market place for medical care. Science 176:488-492, 1972

6. Rickels K: Benzodiazepines: Use and misuse, *In* Klein D, Rabkin J (Eds): Anxiety Revisited. New York, Raven Press, (in press)

7. Manheimer DI, Davidson ST, Balter MB, et al: Popular attitudes and beliefs about tranquilizers. Am J Psychiatry 130: 1246-1253, 1973

8. Uhlenhuth EH, Balter MB, Lipman RS: Minor tranquilizers; clinical correlates of use in an urban population. Arch Gen Psychiatry 35:650-655, 1978

9. Hollister L: Valium: A discussion of current issues. Psychosomatics 28:44-58, 1977

10. Regier DA, Goldberg ID: The de facto U.S. Mental Health Services System. Arch Gen Psychiatry 35:685-693, 1978

11. Ketai R: Family practitioners' knowledge about treatment of depressive illness. JAMA 235:2600-2603, 1976

12. Diagnostic and Statistical Manual of Mental Disorders, 3rd Ed. Washington, DC, American Psychiatric Association, 1980

13. Bielski RJ, Friedel RO: Prediction of tricyclic antidepressant responses. Arch Gen Psychiatry 33:1479-1489, 1976

14. Merskey H: Psychological aspects of pain relief; hypnotherapy; psychotropic drugs, *In* Swerdlow M (Ed): Relief of Intractable Pain. Amsterdam, Elsevier, 1978, pp 21-48

15. Post F: Dementia, depression and pseudo-dementia, *In* Benson FD, Blumer D (Eds): Psychiatric Aspects of Neurologic Disease. New York, Grune & Stratton, 1975, pp 99-120

16. Couch JR, Hassanein RS: Amitriptyline in migrane prophylaxis. Arch Neurol 36:695-699, 1979

17. Shader RI, Greenblatt DJ: Clinical implications of benzodiazepine pharmacokinetics. Am J Psychiatry 134:652-656, 1977

18. Greenblatt DJ, Shader RI, Koch-Weser J: Slow absorption of intramuscular chlordiazepoxide. N Engl J Med 291:1116-1118, 1974

19. Shader RI, Georgotas A, Greenblatt DJ, et al: Impaired absorption of desmethyldiazepam from clorazepate by magnesium aluminum hydroxide. Clin Pharmacol Ther 24:308-315, 1978

20. Berger PA: Antidepressant medications and the treatment of depression, *In* Barchas J, et al (Eds): Psychopharmacology: From Theory to Practice. New York, Oxford Press, 1977, pp 174-207

21. Snyder SH, Yamamura HI: Antidepressants and the muscarinic acetylcholine recepter. Arch Gen Psychiatry 31:236-239, 1977

22. Bigger JT Jr, Kantor SJ, Glassman AH, et al: Cardiovascular effects of tricyclic antidepressant drugs, *In* Lipton MA, DiMascio A, Killam K (Eds): Psychopharmacology; A Generation of Progress. New York, Raven Press, 1978, pp 1033-1046

23. Bigger JT Jr, Giardina EGV, Perel JM, et al: Cardiac antiarrhythmic effect of imipramine hydrochloride. N Engl J Med 296:206-208, 1977

24. Arora RB, Madan BR: Antiarrhythmic action of minor and major tranquilizers. Pharmac Ther 4:633-656, 1979

25. Raisfield IH: Cardiovascular complications of antidepressant therapy. Am Heart J 83:129-133, 1972

26. Vestal RE, Kornhauser DM, Hollifield JW, et al: Inhibition of propranolol by chlorpromazine. Clin Pharmacol Ther 25:19-24, 1979

27. Amsterdam J, Brunswick D, Mendels J: The clinical application of tricyclic antidepressant pharmacokinetics and plasma levels. Am J Psychiatry 137:653-662, 1980

28. Hollister L: Antipsychotic medications and the treatment of schizophrenia, *In* Barchas J, et al (Eds): Psychopharmacology: From Theory to Practice. New York, Oxford Press, 1977, pp 121-149

29. Snyder SH, Greenberg D, Yamamura HI: Antischizophrenic drugs and brain cholinergic receptors. Arch Gen Psychiatry 31: 58-61, 1974

30. Shader RI, Ciraulo DA, Greenblatt DJ: Drug interactions involving psychotropic drugs. Psychosomatics 19:671-681, 1978

31. Bassuk E, Schoonover S: Rampant dental caries in the treatment of depression. J Clin Psychiatry 39:163-165, 1978

32. Heiser JF, Gillin JC: The reversal of anticholinergic drug induced delirium and coma with physostigmine. Am J Psychiatry 127:1050-1052, 1971

33. Granacher RP, Baldessarini RJ: Physostigmine: Its use in acute anticholinergic syndrome with antidepressant and antiparkinson drugs. Arch Gen Psychiatry 32:375-379, 1975

34. Forrest FM, Forrest IS, Serra MT: Modification of chlorpromazine metabolism by some other drugs frequently administered to psychiatric patients. Biol Psychiatry 2:53-58, 1970

35. Greenblatt DJ, Allen MD, MacLaughlin DS, et al: Diazepam absorption: Effect of antacids and food. Clin Pharmacol Ther 24:600-609, 1978

36. Drugs and driving. Med Lett Drugs Ther 19:99-100, 1977

37. Halpern LM: Psychotropic drugs and the management of chronic pain, *In* Bonica J (Ed): Advances in Neurology, Vol. 4. New York, Raven Press, 1974, pp 539-545

38. Kocher R: The use of psychotropic drugs in the treatment of chronic severe pain. Eur Neurol 14:458-464, 1976

39. Adler RH: Psychotropic agents in the management of chronic pain. J Human Stress 4:13-17, 1978

40. Evans-Prosser CDG: The use of pethidine and morphine in the presence of monoamine oxidase inhibitors. Br J Anaesth 40: 279-282, 1968

41. Fann WE, Janowsky DS, Davis JM, et al: Chlorpromazine reversal of the antihypertensive action of guanethidine. Lancet 2:436-437, 1971

42. Petersen V, Hvidt S, Thomsen K, et al: Effect of prolonged thiazide treatment on renal lithium clearance. Br Med J 3:143-145, 1974

43. Chambers J, Kerry RH, Owen G: Lithium used with a diuretic. Br Med J 2:805-806, 1977

44. Berger PA, Barchas JD: Monoamine oxidase inhibitors, *In* Usdin E, Forrest I (Eds): Psychotherapeutic Drugs. New York, Marcel Dekker, 1977, pp 1173-1216

45. Richelson E: Tricyclic antidepressants and neurotransmitter receptors. Psychiatr Ann 9:16-32, 1979

46. Klotz U, Anttila VJ, Reimann I: Cimetidine/diazepam interaction (Letter to Editor). Lancet 2:699, 1979

47. Jefferson JW: A review of the cardiovascular effects and toxicity of tricyclic antidepressants. Psychosom Med 37:160-179, 1975

48. Whitehead W, Blackwell B, Robinson A: Why physicians prescribe benzodiazepines in essential hypertention: A Phase IV study. Biol Psychiatry 12:597-601, 1977

49. Levy BF: Treatment of hypertension with pargyline hydrochloride. Curr Ther Res 8:343-346, 1966

50. Hackett TP, Cassem NA: Reduction of anxiety in the coronary care unit: A controlled double-blind comparison of chlordiazepoxide and amobarbital. Curr Ther Res 14:649-656, 1972

51. Klotz U, Avant GR, Hoyumpa A, et al: The effects of age and liver disease in the disposition and elimination of diazepam in adult man. J Clin Invest 55:347-359, 1975

52. Sellers EM, Greenblatt DJ, Giles HG: Chlordiazepoxide and oxazepam disposition in cirrhosis. Clin Pharmacol Ther 26:240-246, 1979

53. Bennett WM, Singer I, Coggins CJ: A guide to drug therapy in renal failure. JAMA 230:1544-1553, 1974

54. Wetterhus S, Aubert E, Berg CE, et al: The effect of trimipramine (Surmontil®) on symptoms and healing of peptic ulcer; a double-blind study. Scand J Gastroent 12(Suppl 43):33-38, 1977

55. Solow C: Psychotropic drugs in somatic disorders. Int J Psychiat Med 6:267, 1975

56. Whitlock FA: Psychophysiological Aspects of Skin Disease. London, W.B. Saunders, 1976

57. Ananth J: Psychopharmacology and psychosomatic illness. Psychosomatics 16:124-128, 1975

58. Rothstein G, Clarkson DR, Larsen W, et al: The effect of lithium on neutrophil mass and production. N Engl J Med 298: 178-180, 1978

59. Weinstein MR, Goldfield MD: Cardiovascular malformations with lithium use during pregnancy. Am J Psychiatry 132:529-531, 1975

60. Nahas C, Goujard J: Phenothiazines, benzodiazepines and the fetus, *In* Scarpelli EM, Cosmi EV (Eds): Reviews in Perinatal Medicine. New York, Raven Press, 1978, pp 243-280

61. Goldberg HL, DiMascio A: Psychotropic drugs in pregnancy, *In* Lipton MA, DiMascio A, Killam K (Eds): Psychopharmacology; A Generation of Progress. New York, Raven Press, 1978, pp 1047-1055

62. Raskind M, Eisdorfer C: Psychopharmacology of the aged, *In* Simpson LL (Ed): Drug Treatment of Mental Disorders. New York, Raven Press, 1976, pp 237-266

63. Guidotti A: Synaptic mechanisms in the action of benzodiazepines, *In* Lipton MA, DiMascio A, Killam K (Eds): Psychopharmacology; A Generation of Progress. New York, Raven Press, 1978, pp 1349-1357

64. Young S, Kuhar M: Autoradiographic localization of benzodiazepine receptors in the brains of humans and animals. Nature 280:393-395, 1979

65. Salzman C, Kochansky GE, Shader RE, et al: Chlordiazepoxide induced hostility in a small group setting. Arch Gen Psychiatry 31:401-405, 1974

66. Solomon F, White CC, Parron DL, et al: Sleeping pills, insomnia, and medical practice. N Engl J Med 300:803-808, 1979

67. Greenblatt DJ, Shader RI, Franke L: Pharmacokinetics and bioavailability of intravenous, intramuscular and oral lorazepam in humans. J Pharm Sci 68:57-63, 1979

68. Bunney WE, Davis JM: Norepinephrine in depressive reactions. Arch Gen Psychiatry 13:483-494, 1965

69. Goodwin FK, Sack RL: Affective disorders; the catecholamine hypothesis revisited, *In* Usdin E, Snyder S (Eds): Frontiers in Catecholamine Research. New York, Pergamon Press, 1973, pp 1157-1164

70. Maas JW: Biogenic amines and depression: Biochemical and pharmacological separations of two types of depression. Arch Gen Psychiatry 32:1357-1361, 1975

71. Hekimian LJ, Friedhoff AJ, Deever E: A comparison of the onset of action and therapeutic efficacy of amoxapine and amitriptyline. J Clin Psychiatry 39:633-637, 1978

72. Wilson IC, Loosen PT, Pettus CW, et al: A double-blind clinical comparison of amoxapine, imipramine, and placebo in the treatment of depression. Curr Ther Res 22:620-627, 1977

73. Dell AJ: A comparison of maprotiline (Ludiomil®) and amitriptyline. J Int Med Res 5(Suppl):22-24, 1977

74. Fabre LF Jr, McLendon DM, Gainey A: Trazodone efficacy in depression: A double-blind comparison with imipramine and placebo in day-hospital type patients. Curr Ther Res 25:827-834, 1979

75. Brogden RN, Heel RC, Speight TM, et al: Nomifensine: A review of its pharmacological properties and therapeutic efficacy in depressive illness. Drugs 18:1-24, 1979

76. Fabre LF, McLendon DM: Double-blind placebo-controlled study of bupropion hydrochloride (Wellbatrin) in treatment of depressed in-patients. Curr Ther Res 23:393-402, 1978

Brand Name Versus Generic

A WOMAN CAME TO ME and said, "I've gone to a generic from a brand-name antidepressant, and I get far fewer side effects." She came in the next week, and was depressed again. Why? The answer is obvious. The Food and Drug Administration has informed us that between brand-named antidepressants, and certainly between generic and brand-named antidepressants, there is not bioequivalence. It certainly is true that each might have exactly the same number of milligrams of amitriptyline, but it is not true that the filler is the same or the amount of compression is the same. In other words, the bioavailability is not the same. This woman had managed to get a generic product that was not bioequivalent to what she had been taking. She first had a reduction of side effects, which she liked; but then there was a recrudescence of depression, which she did not like. So it is important that you stay with the same brand you start with. I am not making a big pitch here for brand name over generic, but . . . if you are going to use a generic product, sometimes it is very difficult to know which manufacturer of the generic product is being used.

—ALAN BROVAR, MD, *Los Angeles*

Extracted from *Audio-Digest Internal Medicine*, Vol. 27, No. 2, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1577 E. Chevy Chase Drive, Glendale, CA 91206.

Specialty Conference

Participants
LAURENCE A. HARKER, MD
ARTHUR R. THOMPSON, MD, PhD
JOHN M. HARLAN, MD

An edited transcription of a Hematology-Oncology Conference, Division of Hematology, University of Washington School of Medicine, Seattle.

Refer to: Harker LA, Thompson AR, Harlan JM: Thrombosis: Its role and prevention in cardiovascular events—Part I. —Hematology-Oncology Conference, University of Washington (Specialty Conference). West J Med 134:234-241, Mar 1981

Thrombosis: Its Role and Prevention in Cardiovascular Events—Part I

Concepts of Thrombogenesis and Its Prevention

LAURENCE A. HARKER, MD*

WHEREAS NORMAL ENDOTHELIUM is nonreactive with circulating blood, vascular damage initiates platelet and coagulation reactions that result in thrombosis. Since there are several possible mechanisms and pathways for progession in different types of thromboembolic events, drugs that affect one pathway of thrombosis may have little effect on another.

Injury to large arteries exposes basement membrane, collagen and microfibrils with which platelets interact to form an adherent layer of platelets on the endovascular surface. Platelet interaction with collagen leads to the release of adenosine diphosphate (ADP) and activation of the arachidonate pathway to generate thromboxane A_2.[1-5] Both ADP and thromboxane A_2 cause circulating platelets to change shape and adhere to each other and to the platelets already attached to the damaged wall. The growth and stabilization of a thrombus depends in part on the formation of thrombin at the injury site and around the adherent platelet mass. Thrombin can be generated through activation of the extrinsic pathway of coagulation by the tissue thromboplastin that becomes available at the injured site, as well as by activation of the intrinsic coagulation pathway through collagen-mediated activation of factor XII and phospholipoprotein (platelet factor 3) on the platelet surface.[6,7]

Thrombin causes the release of platelet granule contents (including ADP) and activates the arachidonate pathway.[8] Thrombin can also cause aggregation and release through a mechanism that is independent of ADP release or the formation of thromboxane A_2.[9] In addition, polymerizing fibrin stabilizes the accumulating platelet mass; platelet aggregates that are not stabilized by fibrin disaggregate.[10] Clearly, thrombin has an important role in the growth and stability of thrombi.

Epinephrine may also have a part in the formation of intravascular platelet aggregates and thrombi.[11] In addition to its effects on vessel wall tone and on myocardial metabolism, epinephrine potentiates the effects of other aggregating agents, accelerates blood coagulation, and may itself induce platelet aggregation.[12] Therefore, the effects of stress and increased epinephrine levels on the dynamics of platelet interaction with damaged vessel walls and thromboembolism may be important.

There are at least two ways in which the vessel wall may influence thrombosis. The first mechanism involves the formation of prostacyclin (PGI_2,

*Professor of Medicine, Division of Hematology, University of Washington.

Part I of a two-part Specialty Conference. Part II to appear in a subsequent issue.

Reprint requests to: Laurence A. Harker, MD, Division of Hematology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104.

ABBREVIATIONS USED IN TEXT

ADP = adenosine diphosphate
cAMP = cyclic adenosine monophosphate
PDGF = platelet-derived growth factor
PF4 = platelet factor 4
PGI_2 = prostacyclin, prostaglandin I_2
SMC = smooth muscle cell
βTG = β-thromboglobulin
VF = ventricular fibrillation

prostaglandin I_2) by the vessel wall and its inhibition of platelet reactions.[13] In high concentrations, PGI_2 inhibits platelet adherence to damaged vessel walls, thrombin- or collagen-induced aggregation and release, and ADP-induced aggregation.[14] By inhibiting platelet shape change, PGI_2 may also restrict the ability of the platelets to make membrane sites available for acceleration of coagulation. The second mechanism involves the release of plasminogen activator which can cause the localized formation of plasmin that can lyse fibrin around a thrombus and thereby lead to its breakup.[15]

Injury to the endothelium is also postulated to play an important part in atherogenesis.[16] Platelet adhesion and release of a platelet-derived growth factor at sites of endothelial denudation may mediate in part the migration of smooth muscle cells (SMC) from media to the intima and stimulate the proliferation of intimal SMC to form new connective tissue by these cells, and in the case of injury resulting from chronic hyperlipoproteinemia, to deposit lipids within the cells and in the extracellular material. If the injury is a single event, the lesions may be reversible, whereas chronic or repeated injury over an extended period may result in progressive lesion formation and, ultimately, mature atherosclerotic disease. The platelet-derived growth factor (PDGF) is mitogenic for smooth muscle cells, fibroblasts, glial cells and 3T3 cells but not endothelial cells.[17] The growth factor does not appear to be present in plasma in any significant amounts, unless the platelets have undergone the release reaction. Thus, the localized release of this material when platelets adhere to subendothelial connective tissue may be an important factor in smooth muscle cell migration into the intima and proliferation in response to endothelial injury. The macrophage and the endothelial cell itself may represent alternative or additional sources of mitogens that also stimulate smooth muscle cell proliferation.[18,19] Hence, the endothelium might stimulate the underlying smooth muscle cells directly to proliferate in the absence of endothelial denudation. Experimentally, endothelial desquamation and intimal lesion formation has been induced mechanically by surgical procedures, chronic indwelling catheters or intra-arterial balloon catheters; chemically by chronic homocystinemia; immunologically by humoral or cell mediated mechanisms, or by diet-induced chronic hyperlipidemia.[15,16,20-23]

Thrombotic Mechanisms Underlying Cardiac Events

Sudden Death

The immediate factor or factors precipitating terminal dysrhythmias in victims of out-of-hospital ventricular fibrillation (VF) remain largely unidentified at present. The traditional risk factors associated with coronary atherosclerosis per se (smoking, hypertension, hyperlipidemia) are also associated with sudden death—but the risk factors fail to distinguish patients at risk for sudden death as opposed to other coronary events.[24] Postmortem studies of persons who die suddenly of cardiac causes do not show gross thrombosis of coronary arteries.[25] However, advanced atherosclerosis and vessel narrowing of the coronary arteries are characteristic of cases of sudden death. The institution of mobile coronary care systems and the successful resuscitation of many patients experiencing out-of-hospital VF have shown that such episodes are usually not associated with acute myocardial infarction.[26] Additionally, the subgroup of survivors without associated acute myocardial infarction has experienced an extraordinary recurrence of VF in subsequent years.[27] Most patients dying suddenly of cardiac causes out of hospital have coronary atherosclerosis as the only or the dominant cardiac pathological condition.

Many mechanisms for out-of-hospital ventricular fibrillation have been proposed.[28-30] These include (1) abnormal metabolism of myocardial muscle cells, particularly abnormal fatty acid metabolism, (2) tear of an atherosclerotic plaque with formation of a flap which obstructs flow, (3) vasospasm in conjunction with an atherosclerotic plaque which may or may not be associated with vessel wall injury and platelet formation of thromboxane A_2, which causes vasoconstriction and (4) the repeated formation of small mural thrombi that embolize the microcirculation of the

Figure 1.—Electron micrograph of platelet microembolus occluding a small vessel. Interrupted flow in the microcirculation of the heart by platelet thromboemboli may induce ventricular dysrhythmias in patients as demonstrated experimentally in animals. (Reduced from magnification ×6,000.)

myocardium. There is some evidence for all of these pathways although the relative importance of each is unclear.

Experiments with animals have shown that platelet emboli in the microcirculation (Figure 1) can cause ventricular fibrillation and sudden death.[31-34] Adenosine diphosphate infused into the coronary arteries of swine produced circulatory collapse and electrocardiographic evidence of myocardial ischemia. In animals living for more than two hours gross and histological evidence of myocardial infarction was observed. Platelet aggregates per se were directly implicated in that (1) swine previously made thrombocytopenic had no myocardial damage, (2) swine made refractory to ADP (by a previous infusion) were similarly unaffected and (3) platelet aggregates were observed directly in the microvasculature of animals sacrificed during the infusion, although aggregates were not seen in animals with definite infarctions sacrificed after the ADP infusion had been completed. The failure to find aggregates in this latter group, although they were assumed to have caused the infarction, suggests their transience as frank aggregates. Epinephrine infusions in dogs also produced consistent myocardial necrosis or myocytolysis and associated platelet microthrombi in the microvasculature. The induction of mural thrombi in dogs produced sudden death and small foci of myocarditis and necrosis in the myocardium analogous to the lesions observed in humans who die suddenly. Although it seems likely that emboli from mural thrombi in coronary arteries may obstruct the microcirculation of the heart, it is difficult to determine how frequently this occurs in relation to other mechanisms.

A study of the pathological condition of patients dying suddenly in Seattle has shown a high frequency of the pathological finding of patchy myocytolysis, which histologically appeared to antedate the terminal event by 24 hours or more. Platelet aggregates were not identified in the Seattle study, although the histological findings were compatible with platelet microthrombi.[27] However, Haerem[29,30] showed an increased frequency and size of platelet aggregates among patients who had died suddenly with coronary atherosclerosis.

In summary, considerable experimental evidence, including the documentation that platelet microemboli cause tissue damage, as well as the release of vasoactive substances capable of causing coronary artery spasm, suggests a role for platelets in sudden cardiac death. Clinicopathologic studies, including the demonstration of platelet aggregates in the coronary arteries of some patients dying suddenly, help corroborate this thesis.

Myocardial Infarction

Most of the evidence supports the hypothesis that myocardial infarction is caused by thrombotic occlusion of a diseased coronary artery proximal to the site of infarction.[28,35,36] Such thrombi occur in severely diseased arteries, and the mechanisms involved in their formation require extensive stimulation of platelet aggregation for an occlusive thrombus to form. This may imply that a large amount of ADP or thrombin must be formed to cause occlusive thrombi to form at such a site.

More recently Maseri and co-workers[37] showed that "spontaneous" (not catheter- or drug-induced) coronary artery spasm precipitated angina and that repetitive episodes of unstable pain led to myocardial infarction in some cases, and in two such cases in which autopsy studies were done, platelet-fibrin thrombi were found at the sites of previously identified coronary spasm. Oliva and Breckinridge[38] likewise found reversible coronary artery spasm in about 40 percent of all patients in whom coronary angiography was done at the time of acute myocardial infarction. The coronary vasoconstrictive properties of thromboxane A_2 released during platelet aggregation suggests

the possible contribution of platelet hypersensitivity to the coronary artery spasm seen in acute infarction.

Mural Thrombus

Left ventricular mural thrombi have been identified at autopsy in 20 percent to 50 percent of patients following transmural myocardial infarction.[39,40] Activation of the coagulation sequence and the generation of fibrin are important in this process due to the interrupted and static flow conditions in the heart together with a necrotic thrombogenic surface. The relative importance of platelet or fibrin mechanisms and hence the usefulness of platelet-inhibitory drugs or anticoagulants has not been clarified. Patients with congestive cardiomyopathy have a similar frequency of both clinical and autopsy-proved thrombi. Traditional techniques, including contrast left ventricular angiography have not proved sensitive in the detection of mural thrombi. Neither angiography nor two-dimensional echocardiography can identify the extent to which a new thrombus is forming.

Thromboembolism continues to be a significant complication in patients with artificial heart valves, although the risks have been reduced considerably by improved design. Both coagulation and platelet mechanisms are involved.

Blood Tests for Thrombosis

The detection of platelet or coagulation factor activation in vivo may be clinically useful to identify patients at risk and to assess the effects of therapy.

In the setting of stable coronary artery disease a variety of in vitro platelet aggregation studies have given mixed results with most recent studies reporting negative findings.[41-43] Mehta and associates have suggested direct intracoronary consumption of platelets by establishing an aortocoronary sinus concentration gradient in patients with coronary atherosclerosis compared with normal controls.[44] Decreased coronary sinus aggregation to standard stimuli was also shown in the coronary artery disease group, possibly indicative of earlier aggregation in the coronary arteries.

Abnormal platelet consumption in patients with vascular disease reflects platelet activation at sites of damaged vascular endothelium,[45] a circumstance possibly predisposing to downstream microembolization. If platelet microemboli are implicated in the genesis of some cardiac events those patients at high risk might be identified by such studies. Data from Steele and co-workers,[46] our laboratory[47] and more recently from Doyle and associates[48] and Fuster and co-workers[49] have shown shortened in vivo platelet survival in about 50 percent of patients with angiographically documented coronary atherosclerosis and stable angina. Fuster and co-workers also reported shortened platelet survival times among asymptomatic cigarette smokers with a positive family history of coronary artery disease. Platelet survival was returned to normal ranges with administration of the platelet inhibitory agents sulfinpyrazone or dipyridamole. Evidence that this platelet consumption occurred in the coronary vasculature rather than the vasculature at large, however, remains circumstantial since platelet survival studies do not distinguish between coronary artery disease and atherosclerosis generally. We noted improved platelet survival following coronary artery saphenous vein bypass grafting.[47] This observation supports the hypothesis of an intracoronary site of platelet consumption. Steele also showed the stability of these findings over time; in six patients with repeat studies in 3 to 12 months (average 8 months) no changes were found in platelet survival times.[46] In patients following coronary artery bypass grafting, decreased platelet survival has correlated with graft occlusion. Subsequent platelet survival findings failed to distinguish the survivors of ventricular fibrillation from patients with coronary atherosclerosis and angina pectoris, although mean survival time in both patient groups was significantly shortened compared with normal controls.[50] Also, the proportion of shortened survival times in patients after ventricular fibrillation was similar to that seen in patients with stable angina.

Unfortunately, measurements of platelet survival are not sensitive, specific or localizing for vascular lesions. Furthermore, since platelet viability may not be affected by some types of platelet activation, in vivo tests of platelet release might have greater utility. Platelet factor 4 (PF4) and β-thromboglobulin (βTG), platelet specific α-granule proteins, have been shown to be readily released from platelets, and their appearance in plasma can be sensitively detected by radioimmunoassay.[51,52] Moreover, these proteins may reflect the release of PDGF which is also contained in the α granule and which is postulated to be the

mediating mitogen in at least some types of arterial intimal lesion formation. However, blood collection and processing require rigorous attention to detail in order to reduce to a minimum the in vitro release of α-granule contents. We have found that plasma PF4 and βTG levels in normal subjects are consistently less than 3 and 10 ng per ml, respectively, if the blood sample is collected and processed with care.

Organ specific location of active platelet deposition by platelet imaging also holds promise for more specific insights. Employing the ^{111}In-oxine platelet imaging technique, it is possible to detect intracavitary platelet deposition in some survivors of ventricular fibrillation,[53] although intrinsic gamma camera resolution does not allow detection of intracoronary platelet deposition. However, high-resolution, quantitative platelet imaging may be obtainable with emission computerized positron scintigraphy.

Drugs That Modify Platelet Behavior

Assessment of the pharmacology of the drugs that inhibit platelet function and thrombus formation can be considered in four broad categories: (1) drugs that inhibit the arachidonate pathway, (2) drugs that affect platelet cyclic adenosine monophosphate (cAMP) levels, (3) drugs that inhibit thrombin formation and its action and (4) drugs that act through less well-defined mechanisms.[12,13,54]

Drugs That Inhibit the Arachidonate Pathway

Agents that affect this pathway include (1) agents such as aspirin, sulfinpyrazone and indomethacin which all act by inhibiting platelet cyclooxygenase, (2) drugs that block the action of phospholipases and (3) drugs that inhibit thromboxane synthetase. All these drugs inhibit that portion of platelet aggregation and release that is thromboxane A_2 dependent. Blockade of the arachidonate pathway will not affect the process of thrombus formation when it is dependent on other pathways of activation, such as ADP-induced aggregation, adherence of platelets to collagen, the release of granule contents from platelets adherent to collagen, and thrombin-induced aggregation and release.[55,56] In some circumstances thrombin may be more important in the initiation of thrombosis than collagen.

Inhibitors of phospholipases. Drugs that affect the mobilization of arachidonate have been considered to be inhibitors of the phospholipase complex; they include the antimalarial drug mepacrine,[57] and some of the steroidal anti-inflammatory drugs.

Inhibitors of thromboxane synthetase. These inhibitors include imidazole and its derivatives,[58] 9,11-azoprota-5,13-dienoic acid and levamisole, an anthelmintic drug. None of these has been tested for its ability to prevent thrombosis.

Cyclo-oxygenase inhibitors. Drugs that inhibit this enzyme include the nonsteroidal anti-inflammatory drugs such as aspirin, indomethacin, phenylbutazone, ibuprofen, fenoprofen, naproxen and many others, as well as the uricosuric agent sulfinpyrazone.[59,60] Indomethacin is the most potent of these drugs. Under physiological conditions of flow, protein concentration in the suspending medium and hematocrit, aspirin and sulfinpyrazone do not inhibit adherence of the initial layer of platelets to the subendothelium.[56] It must be emphasized, however, that these drugs may inhibit the formation of platelet aggregates on the layer of adherent platelets, most likely by preventing thromboxane A_2 formation. Aspirin, indomethacin and sulfinpyrazone also do not inhibit the release of amine storage granule contents from platelets that adhere directly to collagen or the subendothelium. Released ADP and serotonin from these platelets could contribute to thrombus formation in the presence of the cyclo-oxygenase inhibitors. In addition, the mitogenic factor released from platelets stimulates smooth muscle cell proliferation at a site of injury, and since aspirin and sulfinpyrazone do not inhibit release of granule contents from the adherent platelets it is not surprising that these drugs do not prevent smooth muscle cell proliferation in response to vessel damage.[61]

An effect of these drugs which might be beneficial is their ability to prevent thromboxane A_2-mediated vasoconstriction. An additional beneficial consequence is that thromboemboli do not readily lodge and persist in the microcirculation. Relatively little is known about this possibility but it may be relevant to transient attacks of cerebral ischemia.[62] In the myocardial circulation, there is a possibility that these drugs may affect platelet aggregate formation and thromboxane A_2 formation. In dogs with experimentally stenosed coronary arteries, both aspirin and sulfinpyrazone inhibit the formation of platelet plugs and the occurrence of fatal arrhythmias. Studies with

ischemic dog and cat myocardium have shown that sulfinpyrazone and aspirin can prevent ventricular fibrillation caused by ischemia.[32-34]

The effects of low doses of aspirin on the ability of platelets to form thromboxane A_2 are irreversible since acetylation of the cyclo-oxygenase is permanent.[59] In contrast to the irreversible effects on platelets, aspirin's effect on the cells of the vessel wall is not permanent because these cells can reform cyclo-oxygenase. If PGI_2 does have a role in limiting some forms of thrombosis, once-daily administration of aspirin (rather than more frequent administration) would seem to be a rational approach to inhibiting the ability of platelets to form thromboxane A_2 without completely blocking PGI_2 production by the vessel wall. However, the situation is complicated by the fact that there are some antithrombotic effects of aspirin that are independent of cyclo-oxygenase inhibition and require multiple larger doses throughout the day.[63,64]

It is well known that before menopause, women have a lower frequency of the clinical complications of atherosclerosis than men of the same age. This has been attributed to a protective effect of estrogens and there is some experimental support for this view. Results of clinical trials have now raised the possibility that the beneficial effects of aspirin and sulfinpyrazone may be much less apparent in women than in men.[62] Future clinical trials should be designed with this possibility in mind.

Agents That Increase cAMP Levels

When the cAMP level in platelets is raised, many platelet functions are inhibited. Platelet cAMP is elevated by agents that stimulate adenylate cyclase and drugs which inhibit platelet phosphodiesterase by preventing the breakdown of cAMP in platelets.[65] Adenylate cyclase is stimulated by the prostaglandins PGI_2, PGD_2 and PGE_1. PGI_2 can be produced by the cells of the vessel wall in response to stimulation by injury, thrombin, bradykinin or angiotensin II.[66] PGD_2 is one of the products formed from arachidonate in platelets. Several studies have shown that the combination of PGI_2 and PGE_1 with a phosphodiesterase inhibitor strongly inhibits platelet functions.

Dipyridamole is a potentially interesting drug because it inhibits platelet phosphodiesterase and thereby raises cAMP levels. However, other effects such as vasodilation may account for some of its actions in some situations in which it has been shown to be beneficial.[67] It has been suggested that the apparent greater effects of dipyridamole in vivo compared with in vitro effects are related to synergism between dipyridamole and PGI_2 on cAMP.[68]

Some of the pyrimido-pyrimidine drugs have been shown to inhibit thrombus formation in injured vessels of experimental animals and extracorporeal shunts, and to lessen myocardial necrosis caused by epinephrine infusion. Dipyridamole does inhibit platelet adherence to collagen, the subendothelium artificial surfaces and diminishes the extent of atherosclerosis induced in monkeys by the administration of homocysteine.[69-72]

Agents That Inhibit Thrombin

The effects of thrombin on platelets and on fibrin formation can be prevented by inhibiting its generation with anticoagulants. Heparin, through its effect on antithrombin III, also inhibits early steps of the coagulation sequence.

Reports of the effects of heparin on platelet reactions are complex and contradictory,[73] perhaps in part because of the variability among different commercially available heparin preparations. In vitro, heparin prevents the effects of thrombin on platelets, but may potentiate or inhibit aggregation and release induced by other aggregating agents. It may itself cause platelet aggregation, result in thrombocytopenia or even arterial embolization. It has been suggested that some of the unusual adverse effects of heparin therapy may in part relate to the heparin antagonism of vascular PGI_2.[74] When well-defined anticoagulant fractions of heparin become available for more extensive tests, it will be necessary to reassess the effects of heparin in a variety of experimental and clinical situations.

Other Agents That Inhibit Platelet Function and Thrombus Formation

A large group of other agents have been shown to inhibit platelet reactions and thrombus formation although the mechanism of action of many of them is not yet well defined. Some may change the sensitivity of the platelet membrane to stimulation by altering membrane fluidity, decreasing the availability of membrane receptors or inhibiting phospholipase activation.

Propranolol and other β-blockers. Administration of propranolol to patients with angina pec-

toris is reported to reduce their increased platelet sensitivity to ADP-induced aggregation and to improve exercise tolerance.[75]

Clofibrate and halofenate. These drugs lower serum lipids. They also inhibit collagen-induced aggregation and the second phase of ADP- or epinephrine-induced aggregation.[76] Both drugs decrease the sensitivity of platelets to aggregating agents in patients with familial hyperbetalipoproteinemia.[77]

Ticlopidine. Ticlopidine is interesting because its effects are manifest after 24 hours following administration and last for several days after administration of the drug is stopped. It also inhibits the primary phase of ADP-induced aggregation,[78] prolongs shortened platelet survival in rats and inhibits intimal proliferation in the rabbit aorta from which the endothelium has been removed.[78,79]

Other drugs. Vitamin E inhibits collagen-induced aggregation and the second phase of aggregation induced by ADP or epinephrine in citrated human platelet-rich plasma.[80] Many other drugs have been shown to have inhibitory effects on platelet functions, but in many cases the mode of action is not established. These drugs include penicillin and related antibiotics; antihistamine and antiserotonin drugs such as cyproheptadine, promethazine, lidoflazine and suloctidil; diuretics such as furosemide; tricyclic compounds such as imipramine, amitriptyline and chlorpromazine; nitrofurantoin; pyridinolcarbamate; nitroprusside, and alcohol.

Combinations of Drugs

Since several mechanisms may be involved in thrombus formation, combinations of drugs that inhibit different mechanisms may be beneficial. There is some indication that a combination of a drug that inhibits platelet functions with an oral anticoagulant or heparin may be beneficial but no large clinical trials have been undertaken. Dipyridamole and aspirin appear to potentiate the antithrombotic effects of each other.

REFERENCES

1. Baumgartner HR, Muggli R: Adhesion and aggregation: Morphological demonstration and quantitation in vivo and in vitro, *In* Gordon JL (Ed): Platelets in Biology and Pathology. Amsterdam, Elsevier/North-Holland Biomedical Press, 1976, pp 23-60

2. Hovig T: Release of a platelet aggregating substance (adenosine diphosphate) from rabbit blood platelets induced by saline "extract" of tendons. Thromb Diath Haemorrh 9:264-278, 1963

3. Smith JB, Ingerman C, Kocsis JJ, et al: Formation of an intermediate in prostaglandin biosynthesis and its association with the platelet release reaction. J Clin Invest 53:1468-1472, 1974

4. Svensson J, Hamberg M, Samuelsson B: On the formation and effects of thromboxane A_2 in human platelets. Acta Physiol Scand 98:285-294, 1976

5. Bell RL, Kennerly DA, Stanford N, et al: Diglyceride lipase: A pathway for arachidonate release from human platelets. Proc Natl Acad Sci USA 76:3238-3241, 1979

6. Nemerson Y, Pitlick FA: The tissue factor pathway of blood coagulation. Prog Hemost Thromb 1:1-37, 1972

7. Zwaal RFA: Membrane and lipid involvement in blood coagulation. Biochem Biophys Acta 515:163-205, 1978

8. Bills TK, Smith JB, Silver MJ: Selective release of arachidonic acid from the phospholipids of human platelets in response to thrombin. J Clin Invest 60:1, 1977

9. Charo IF, Feinman RD, Detwiler TC: Interrelations of platelet aggregation and secretion. J Clin Invest 60:866-873, 1977

10. Niewiarowski S, Regoeczi E, Stewart GJ, et al: Platelet interaction with polymerizing fibrin. J Clin Invest 51:685-700, 1972

11. Haft JI, Kranz PD, Albert LJ, et al: Intravascular platelet aggregation in the heart induced by norepinephrine—Microscopic studies. Circulation 46:698-708, 1972

12. Mustard JF, Packham MA: Factors influencing platelet function: Adhesion, release, and aggregation. Pharmacol Rev 22:97-187, 1970

13. Moncada S, Vane JR: Arachidonic acid metabolites and the interactions between platelets and blood vessel walls. N Engl J Med 300:1142-1147, 1979

14. Weiss HJ, Turitto VT: Prostacyclin (prostaglandin I_2, PGI_2) inhibits platelet adhesion and thrombus formation on subendothelium. Blood 53:244-250, 1979

15. Majno G, Joris I: Endothelium 1977: A review, *In* Chandler AB, Eurenius K, McMillan GC, et al (Eds): The Thrombotic Process in Atherogenesis—Adv Exp Med Biol, Vol 104. New York, Plenum Press, 1978, pp 169-225

16. Ross R, Harker LA: Hyperlipidemia and atherosclerosis—Chronic hyperlipidemia induces lesion initiation and progression by endothelial cell desquamation and lipid accumulation. Science 193:1094-1100, 1976

17. Wall RT, Harker LA, Quadracci LJ, et al: Factors influencing endothelial cell proliferation in vitro. J Cell Physiol 96:203-214, 1978

18. Gajdusek C, Schwartz SM, DiCorleto P, et al: Endothelial cell derived mitogenic activity. Fed Proc (abst) 38:1075, 1979

19. Leibovich SJ, Ross R: A macrophage-dependent factor that stimulates the proliferation of fibroblasts in vitro. Am J Pathol 84:501-513, 1976

20. Moore S: Thromboatherosclerosis in normolipemic rabbits: A result of continued endothelial damage. Lab Invest 29:478-487, 1973

21. Harker LA, Slichter SJ, Scott CR, et al: Homocystinemia: Vascular injury and arterial thrombosis. N Engl J Med 291:537-543, 1974

22. Friedman RJ, Stemerman MB, Wenz B, et al: The effect of thrombocytopenia on experimental arteriosclerotic lesion formation in rabbits—Smooth muscle cell proliferation and re-endothelialization. J Clin Invest 60:1191-1201, 1977

23. Minnick CR, Murphy GE: Experimental induction of atherosclerosis by the synergy of allergic injury to arteries and lipid rich diet—II. Effect of repeatedly injected foreign protein in rabbits fed a lipid-rich, cholesterol-poor diet. Am J Pathol 73:265-300, 1973

24. Kannel WB, Doyle JT, McNamara PM, et al: Precursors of sudden coronary death: Factors related to the incidence of sudden death. Circulation 51:606-613, 1975

25. Schwartz CJ, Chandler AB, Gerrity RG, et al: Clinical and pathological aspects of arterial thrombosis and thromboembolism, *In* Chandler AB, Eurenius K, McMillan GC (Eds): The Thrombotic Process in Atherogenesis—Adv Exp Med Biol, Vol 104. New York, Plenum Press, 1978, pp 111-126

26. Baum RS, Alvarez H III, Cobb LA: Survival after resuscitation from out-of-hospital ventricular fibrillation. Circulation 50: 1231-1235, 1974

27. Cobb LA, Baum RS, Alvarez H III, et al: Resuscitation from out-of-hospital ventricular fibrillation: 4 years follow-up. Circulation 52(Suppl III):223-228, 1975

28. Crawford T: Pathology of Ischaemic Heart Disease. London, Butterworths, 1977

29. Haerem JW: Mural platelet microthrombi and major acute lesions of main epicardial arteries on sudden coronary death. Atherosclerosis 19:529-541, 1974

30. Haerem JW: Myocardial lesions in sudden, unexpected coronary death. Am Heart J 90:562-568, 1975

31. Jorgensen L, Rowsell HC, Hovig T, et al: Adenosine diphosphate induced platelet aggregation and myocardial infarction in swine. Lab Invest 17:616-644, 1967

32. Haft JI, Gershengorn K, Kranz PD, et al: Protection against epinephrine-induced myocardial necrosis by drugs that inhibit platelet aggregation. Am J Cardiol 30:838-843, 1972

33. Folts JD, Crowell EB, Rowe GG: Platelet aggregation in partially obstructed vessels and its elimination with aspirin. Circulation 54:365-370, 1976

34. Moschos CB, Haider B, De La Cruz C Jr, et al: Antiarrhythmic effects of aspirin during nonthrombotic coronary occlusion. Circulation 57:681-684, 1978

35. Chandler AB, Chapman I, Erhardt LR, et al: Coronary thrombosis in myocardial infarction—Report of a workshop on the role of coronary thrombosis in the pathogenesis of acute myocardial infarction. Am J Cardiol 34:823-833, 1974

36. Fulton WFM, Sumner DJ: Causal role of coronary artery thrombotic occlusion in myocardial infarction: Evidence of stereoarteriography, serial sections and ^{125}I fibrinogen autoradiography. Am J Cardiol 39:322, 1977

37. Maseri A, L'Abbate A, Baroldi G, et al: Coronary vasospasm as a possible cause of myocardial infarction—A conclusion derived from the study of "preinfarction" angina. N Engl J Med 299:1271-1277, 1978

38. Oliva PB, Breckinridge JC: Arteriographic evidence of coronary arterial spasm in acute myocardial infarction. Circulation 56:366-374, 1977

39. Report of the Working Party on Anticoagulant Therapy in Coronary Thrombosis to the Medical Research Council: Assessment of short-term anticoagulant administration after cardiac infarction. Br Med J 1:335-342, 1969

40. Veterans Administration Hospital Investigators: Anticoagulants in acute MI—Results of cooperative clinical trial. JAMA 225:724-729, 1973

41. Hampton JR, Gorlin R: Platelet studies in patients with coronary artery disease and in their relatives. Br Heart J 34: 465-471, 1972

42. Steele PP, Weily HS, Davies H, et al: Platelet function studies in coronary artery disease. Circulation 48:1194-1200, 1973

43. Wu KK, Hoak JC: A new method for the quantitative detection of platelet aggregates in patients with arterial insufficiency. Lancet 2:924-926, 1974

44. Mehta J, Mehta P, Pepine CJ: Platelet aggregation in aortic and coronary venous blood in patients with and without coronary disease—3. Role of tachycardia stress and propranolol. Circulation 58:881-886, 1978

45. Harker LA, Slichter SL: Platelet and fibrinogen consumption in man. N Engl J Med 287:999-1005, 1972

46. Steele P, Rainwater J, Vogel R, et al: Platelet-suppressant therapy in patients with coronary artery disease. JAMA 240:228-231, 1978

47. Ritchie JL, Harker LA: Platelet and fibrinogen survival in coronary atherosclerosis—Response to medical and surgical therapy. Am J Cardiol 39:595-598, 1977

48. Doyle DJ, Chesterman CN, Cade JF, et al: Plasma concentrations of platelet-specific proteins correlated with platelet survival. Blood 55:82-84, 1980

49. Fuster V, Brandenburg RO: Cigarette smoking, positive family history and shortened platelet survival as predictors of coronary artery disease under age of 50. Proc Assoc Univ Cardiologists, Phoenix, AZ, 1978

50. Ritchie JL, Cobb LA, Harker LA: Platelet survival in patients previously resuscitated from out-of-hospital ventricular fibrillation. J Lab Clin Med 63:310-315, 1979

51. Bolton AE, Ludlam CA, Pepper DS, et al: A radioimmunoassay for platelet factor 4. Thrombos Res 8:51-58, 1976

52. Kaplan KL, Nossel HL, Drillings M, et al: Radioimmunoassay of platelet factor 4 and β-thromboglobulin: Development and application to studies of platelet release in relation to fibrinopeptide A generation. Br J Haematol 39:129-146, 1978

53. Goodwin DA, Bushberg JT, Doherty PW, et al: Indium-111-labeled autologous platelets for location of vascular thrombi in humans. J Nucl Med 19:626-634, 1978

54. Packham MA, Mustard JF: Pharmacology of platelet-affecting drugs, *In* Braumwald E, Weiss HJ, Mustard JF, et al (Eds): The Role of Platelets in Coronary Artery Disease. NIH document

55. Packham MA, Kinlough-Rathbone RL, Reimers HJ, et al: Mechanisms of platelet aggregation independent of adenosine diphosphate, *In* Silver MJ, Smith JB, Kocsis JJ (Eds): Prostaglandins in Hematology. New York, Spectrum Pub 1977, pp 247-276

56. Weiss HJ, Tschopp TB, Baumgartner HR: Impaired interaction (adhesion-aggregation) of platelets with the subendothelium in storage-pool disease and after aspirin ingestion—A comparison with von Willebrand's disease. N Engl J Med 293:619-623, 1975

57. Blackwell GJ: Phospholipase A_2 and platelet aggregation. *In* Galli C, Galli G, Procellati G (Eds): Advances in Prostaglandin and Thromboxane Research, Vol 3. New York, Raven Press, 1978, pp 137-142

58. Moncada S, Bunting S, Mullane K, et al: Imidazole: Selective inhibitor of thromboxane synthetase. Prostaglandins 13:611-618, 1977

59. Roth GJ, Majerus PW: Acetylation of prostaglandin synthetase by aspirin, *In* Silver MJ, Smith JB, Kocsis JJ (Eds): Prostaglandins in Hematology. New York, Spectrum Pub, 1977, pp 345-360

60. Ali M, McDonald JWD: Reversible and irreversible inhibition of platelet cyclooxygenase and serotonin release by nonsteroidal antiinflammatory drugs. Thromb Res 13:1057-1065, 1978

61. Clowes AW, Karnovsky MJ: Failure of certain antiplatelet drugs to affect myointimal thickening following arterial endothelial injury in the rat. Lab Invest 36:452-464, 1977

62. The Canadian Cooperative Study Group: A randomized trial of aspirin and sulfinpyrazone in threatened stroke. N Engl J Med 299:53-59, 1978

63. Slichter SJ, Harker LA: Preparation and storage of platelet concentrates—II. Storage variables influencing platelet viability and function. Br J Haematol 34:403-419, 1976

64. Scharrer I, Gundlach E, Schultze U, et al: In vitro and in vivo investigations on the protein binding of different aggregation inhibitors. IV International Congress on Thrombosis and Haemostasis. Abstract #360, p 395, 1973

65. Haslam RJ, Davidson MML, Davies T, et al: Regulation of blood platelet function by cyclic nucleotides. Adv Cyclic Nucleotide Res 9:533-552, 1978

66. Blumberg AL, Denny SE, Marshall GR, et al: Blood vessel hormone interactions: Angiotensin, bradykinin, and prostaglandins. Am J Physiol 232:H305-H310, 1977

67. Roberts AJ, Jacobstein JG, Cipriano PR, et al: Effectiveness of dipyridamole in reducing the size of experimental myocardial infarction. Circulation 61:228-235, 1980

68. Moncada S, Korbut R: Dipyridamole and other phosphodiesterase inhibitors act as antithrombotic agents by potentiating endogenous prostacyclin. Lancet 1:1286-1289, 1978

69. Moncada S, Flower RJ, Russell-Smith N: Dipyridamole and platelet function. Lancet 2:1257-1258, 1978

70. Kinlough-Rathbone RL, Groves HM, Cazenave JP, et al: Effect of dipyridamole and aspirin on platelet adherence to damaged rabbit aortas in vitro and in vivo. Fed Proc 37-260, 1978

71. Harker LA, Hanson SR: Experimental arterial thromboembolism in baboons—Mechanism, quantitation, and pharmacologic prevention. J Clin Invest 64:559-569, 1979

72. Harker LA, Ross R, Slichter SJ, et al: Homocystine-induced arteriosclerosis—The role of endothelial cell injury and platelet response in its genesis. J Clin Invest 58:731-741, 1976

73. Salzman EW, Rosenberg RD, Smith MH, et al: Effect of heparin and heparin fractions on platelet aggregation. J Clin Invest 65:64-73, 1980

74. Eldor A, Weksler BB: Heparin and dextran sulfate antagonize PGI_2 inhibition of platelet aggregation. Thromb Res 16: 617-628, 1979

75. Frishman WH, Christodoulou J, Weksler B, et al: Abrupt propranolol withdrawal in angina pectoris: Effects on platelet aggregation and exercise tolerance. Am Heart J 95:169-179, 1978

76. Favis GR, Colman RW: The action of halofenate on platelet shape change and prostaglandin synthesis. J Lab Clin Med 92:45-52, 1978

77. Colman RW: Platelet function in hyperbetalipoproteinemia. Thromb Haemostas 39:284-293, 1978

78. Wilkinson AR, Hawker RJ, Hawker LM: The influence of antiplatelet drugs on platelet survival after aortic damage or implantation of a Dacron arterial prothesis. Thromb Res 15:181-189, 1979

79. Reece AH, Walton PL: Inhibition on intimal proliferation of rabbit aorta by ticlopidine. Thromb Haemostas 42:367, 1979

80. Steiner M, Anastasi J: Vitamin E. An inhibitor of the platelet release reaction. J Clin Invest 57:732-737, 1976

Refer to: Tierney LM Jr: Aortoenteric fistula—Medical Staff Conference, University of California, San Francisco. West J Med 134:242-247, Mar 1981

Aortoenteric Fistula

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr, Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR. SLEISENGER:* *In this conference we will consider an unusual but catastrophic cause of gastrointestinal bleeding which presents special diagnostic problems for internists. Dr. Larry Tierney will review the subject of aortoenteric fistula.*

DR. TIERNEY:† Major bleeding from the lower and upper gastrointestinal tract is one of the most common medical emergencies encountered by internists. A fistula which occurs between the aorta and the gastrointestinal tract is an uncommon cause of such bleeding. Modern vascular surgical procedures, which allow for aortic reconstruction, and increasing numbers of patients with vascular disease are factors indicating that this entity will become more common. Most reports on this subject are found in the surgical literature, despite the fact that internists are more likely to see patients with gastrointestinal bleeding at the time of initial presentation. This review will outline theories of pathogenesis of aortoenteric fistula, describe its clinical features, and discuss the approach to diagnosis and treatment.

History

Cooper first described this entity pathologically in 1829, and scattered reports appeared subsequently. Until the 1950's all cases were primary—that is, they were characterized by a diseased native aorta eroding into contiguous gastrointestinal tract. Though this usually meant an abdominal aortic aneurysm penetrating the duodenum, primary aortoesophageal fistulas due to expanding thoracic luetic aneurysms were also seen in the preantibiotic era. Since 1950, however, reconstructive vascular surgical procedures have become more available for aneurysm resection and for replacement of severely atherosclerotic distal aortas and iliofemoral systems. As a result, fistulas arising from the prosthetic vessels began to appear. Brock first reported this secondary type of aortoenteric fistula in 1953, after aortic homografting.[1] Indeed, most aortoenteric fistulas encountered at present are of the secondary variety. While in modern clinical practice about 80 percent of these secondary fistulas occur between the aorta and the duodenum, particularly the third portion, the potential for this complication to develop exists wherever an operated large artery makes contact anatomically with a hollow viscus. Thus, similar anatomic circumstances predispose to primary and secondary fistulas.

Epidemiology

The incidence of these events cannot be stated with certainty. Because abdominal aortic aneurysm often exists in an asymptomatic form, it is impossible to arrive at statistics showing the percentage of aneurysms that go on to fistulize as a pri-

*Marvin H. Sleisenger, MD, Professor and Vice Chairman, Department of Medicine; Chief of the Medical Service, Veterans Administration Hospital, San Francisco.

†Lawrence M. Tierney, Jr, MD, Associate Professor of Medicine; Assistant Chief, Medical Service, Veterans Administration Hospital, San Francisco.

mary event. Nevertheless, it seems logical that this would be a very small number, one much less than that for secondary aortoenteric fistulas (AEF). Data for incidence of the latter exist in surgical series gleaned from consecutive aortic reconstructions, with the cases of patients in such series being followed over time for complications. Only one such consecutive analysis, that of Elliott and co-workers, quotes figures for each type of reconstruction—that is, for aneurysm replacement versus aortoiliac repair.[2] In their experience in over 2,000 cases at the Henry Ford hospital, they found an incidence of AEF of 1.7 percent after emergency aneurysm replacement, 0.7 percent after elective aneurysmectomy and 0.2 percent after graft placement for aortoiliac disease. Most subsequent series, such as that of Kleinman and associates, merely report AEF after graft placement without indicating the reason for the initial operation.[3] However, anecdotal information from this institution leaves the impression that AEF is considered far less likely to occur after aneurysm replacement than after aortoiliac reconstruction, an observation which differs from that cited. Part of the difficulty in compiling this kind of information and in elucidating the full understanding of the problem results from the fact that most reports describe one or two patients; since 1963, only a handful of papers have concerned more than five patients. One might assume that the total number of AEF will rise because of a larger patient population undergoing vascular repair, but that the percentage incidence will decline owing to improved techniques and to prosthetic material of better durability.

Factors contributing to increased incidence of secondary AEF in the past have included the use of aortic homograft and also of silk sutures. Neither of these is employed today, and only rare reports of synthetic graft failure exist. Early reoperation for graft failure also seems to enhance risk, as do development of anastomotic false aneurysm, postoperative hypertension and any type of enterotomy at the original operation.[3] Finally, and perhaps most important, failure to establish adequate separation of graft and intestine by insertion of retroperitoneal tissue, peritoneum or synthetic material between these structures has been identified retrospectively as a frequent contributor to the development of secondary AEF.

Pathogenesis

Any theory of pathogenesis must reconcile (1) the epidemiologic data just described, (2) the occurrence of these fistulas usually with, but occasionally without, previous vascular surgical procedure and (3) the anatomic preference for fistulization to the retroperitoneal part of the duodenum, but the documented presence of fistulas at numerous locations where intestines and vessels touch. It is likely that most aortoenteric fistulas are multifactorial, with infection and mechanical tissue trauma leading to necrosis being the two processes of most import. While AEF could result from either alone, most require both; the clinical features to be discussed may give clues to which plays the dominant role in given cases.

It is not difficult to envision how mechanical stress could lead to erosion of the gut from without. The site of most AEF, either primary or secondary, is the duodenum; in primary AEF due to atherosclerotic aneurysms of the abdominal aorta, this is nearly always the location, with a smaller but still large percentage of the secondary type noted there as well. The third portion of the duodenum is covered on its anterior surface by the peritoneum, and lies in essence retroperitoneally, superficial to the aorta just distal to the renal arteries. More than 90 percent of atherosclerotic aneurysms arise here and, likewise, this location is the site of the proximal surgical repair in both aneurysm replacement and aortoiliac rebuilding. The duodenum is relatively fixed here and receives the impact of each aortic pulsation, even in health.

With aneurysm, the increasing radius of the diseased aorta produces rising wall tension via the LaPlace relationship, where $T = Pr$ (tension equals pressure times radius). The rigid duodenal wall may undergo pressure necrosis and be entered by the aorta, which in turn is subjected to enzymatic or bacterial action (or both) at a time when rupture may be imminent.

The erosive power of any aneurysm enlarged under arterial pressure is perhaps more forcefully dramatized by luetic thoracic aneurysms of old, which were known to be capable of eroding through the sternum and rupturing externally. Surgeons who have inspected large atherosclerotic aneurysms at the time of operation have felt it surprising that primary AEF are not more common, so tightly adherent is the vessel to the intestine. The propensity for aneurysm rupture to occur posteriorly and laterally into the retroperitoneum, may account for this. In any event, these considerations make possible a pathogenesis of *primary* AEF requiring little else save the deranged hemo-

dynamics, and this will be seen to have therapeutic implications.

In secondary AEF aneurysmal dilatation is not present, and thus wall tension is normal in the aortic prosthesis. However, many physicomechanical derangements, likely damaging to the bowel, are induced by operation and contribute to the development of secondary AEF. To replace a diseased aorta, considerable handling of the duodenum, which may have already been compromised by the vessel preoperatively, is obligatory. Dissection may prove difficult, but the surgeon must be meticulous in separating aorta from gut and maintaining same after placement of the prosthesis. Vascular supply may be impaired locally, and histologic examination of the intestine from such patients discloses stripped adventitia, flattened villi and cholesterol emboli in the small vessels. Intuitively one might predict that a duodenum so damaged would be more prone to a local perforation or erosion by a nearby vessel. Similarly, the postoperative reparative process and foreign body reaction to the graft are other sources of mechanically mediated tissue damage. In the early days of vascular surgical procedures both homografts and silk sutures underwent more rapid degeneration under these stresses, and a fistulous leak would begin from any point in the graft. Modern materials seldom if ever fail for purely physical reasons, but the prolene sutures used widely in vascular work have been reported capable of perforating nearby intestine if their ends are not clipped off short and smoothed by cautery.

In contrast to primary AEF, occurring for practical purposes only in the duodenum, it can be appreciated that tissue damage related to an operation could render bowel less viable at the distal repair line much as it could proximally, allowing secondary AEF to be found elsewhere in the intestine, without attributing a major role to the pulsatile forces not readily transmissible to intraperitoneal parts of the bowel. A final mechanical factor leading to secondary AEF is pseudoaneurysm at the suture lines. This, too, has become less common with newer techniques and materials.

The other major element in pathogenesis is infection, which many surgeons feel is ubiquitous in secondary AEF—even in cases which present many years after placement of the graft. In the only experimental model of secondary AEF, Busuttil and co-workers proposed that these fistulas developed in dogs artificially infected after aortic replacement with Dacron grafts.[4] Though this work has met with some criticism regarding its dissimilarity to human disease, it serves to underscore the concern surgeons have about infection in this clinical situation. In patients with secondary AEF it is easy to see how graft contamination at the time of operation could lead to anastomotic breakdown. This probably accounts for the higher incidence of AEF after emergent rather than elective aneurysm repair, and for the similar increase noted when enterotomy of any type is carried out during the vascular reconstruction. To imply infection as the cause does not require direct contamination in most cases, but it does necessitate participation of the mechanical abnormalities outlined above. This scenario would hold that such damage to the intestine would ultimately produce small areas of perforation. This perforation would be local and small, and would take place at the site of contiguous vascular structure. Adherent interposed peritoneum, omentum or retroperitoneal scarring would serve to keep infection confined, and clinical signs of diffuse peritonitis would not be present.

Other observations underscore the role of infection in secondary AEF. Most notable are the reports of culture results taken at the time of surgical exploration of patients found to have this disorder. Although few data are available for large series from the same institution, Rosenthal and associates[5] have studied the cases of several patients with clinically typical secondary AEF. In all of the patients, blood and tissues from operative sites were cultured, and, in each, organisms were recovered which were compatible with enteric origins of these organisms. All patients in this group were febrile, but little information exists from other reports concerning the frequency of this finding; most recently Kiernan and co-workers noted fever in 10 of 20 patients they analyzed.[6] The fact that in Rosenthal's patients the same organisms grew from both specimens, as well as there being microbiological characteristics of these organisms consistent with an upper gastrointestinal tract source diminish the likelihood of seeding from remote infection; Kiernan noted similar findings. Contrasting slightly are unpublished data from our hospitals, which show that *Staphylococcus epidermidis* organisms appear as a pathogen in otherwise unremarkable cases of secondary AEF; this suggests that introduction of these bacteria occurred at operation, despite relatively long de-

lays (greater than two years) until the clinical expression of the fistula.

Indeed, infection occupies a central position in a clinicopathologic separation of secondary AEF into two general types proposed first by DeWeese and Fry in 1962[7] and most recently reviewed by O'Mara and Imbembo.[8] The first is a genuine fistula taking place at the suture line via the mechanisms proposed here, resulting in features dominated by gastrointestinal hemorrhage. The second type, called "paraprosthetic enteric fistula" by Elliot, Smith and Szilagyi,[2] consists of communication between the gastrointestinal tract and the external surface of the synthetic vascular prosthesis without true penetration into the aortic lumen. Where this latter has been reported with true secondary AEF, it is approximately one fifth as common, and its clinical features are those of smoldering localized infection and not of bleeding. O'Mara and Imbembo believe that these paraprosthetic-enteric fistulas are distinct clinical entities but at the same time represent a step in the formation of true AEF. In each, diminished tissue viability of the intestinal wall permits perforation and escape of bacteria into the retroperitoneum. In most cases, AEF occurs as a common consequence; however, presence of the aforementioned tissue interposed between graft and intestine may inhibit or prevent direct dissection of organisms to the graft, with resultant paraprosthetic-enteric fistula and its supposedly unique clinical features. Presumably, if left untreated, more characteristics of classical AEF emerge in these patients, and such a progression has been witnessed by O'Mara and Imbembo.

Pathogenesis of AEF, therefore, may have important mechanical *and* infectious components, with the dominant clinical profile a function of which of the two is preeminent. In primary AEF, mechanical forces may account for the entire problem; in secondary, the most tenable hypothesis allows roles for each.

Clinical Features

Clinically, most patients with AEF, both primary and secondary, come to a physician's attention because of gastrointestinal bleeding. The typical patient is male, about 60 years old, often with evidence for cerebral and coronary vascular disease. Primary AEF causes more difficulty in diagnosis because there will be no history of vascular surgical procedures. These patients do, however, manifest symptoms and signs of expanding abdominal aneurysm, with abdominal or back pain (or both) and a palpable pulsatile mass in 70 percent. Because of the bleeding the pain may escape careful analysis, and physical examination can be too cursory while the physician is pursuing the diagnostic evaluation. Despite the rarity of primary AEF, it is not unreasonable given available therapies that clinicians consider this diagnosis in every patient in the proper age range with unexplained intestinal bleeding.[9]

In secondary AEF there is by definition a history of previous vascular surgical procedures; many observers have stated that the first consideration in gastrointestinal bleeding with such a background should be secondary AEF. The time from vascular operation to clinical penetrance of the fistulas is widely variable, from days or weeks up to 15 years, with an average from grouped series of about four to five years. These patients also typically report abdominal pain with back radiation, but a pulsatile mass is not felt. Given the pathogenetic role of enteric bacteria in secondary AEF, clinical evidence of infection is variably present. Regrettably, of larger series only Kiernan comments on the percent of patients with fever,[6] and many individual case reports mention it. Likewise, where sought for, operative site cultures, and those of blood, grow enteric organisms in half or more. On occasion, infectious aspects will be the dominant feature; this can take place with the increasingly rare event of direct contamination at initial operation, in which case it becomes manifest within weeks. Symptoms of low grade fever, malaise, weight loss and mild anemia may be central in paraprosthetic-enteric fistula, before development of bona fide AEF with bleeding. Rare but interesting infectious complications of secondary AEF include multicentric osteomyelitis of the bones of the lower extremities[10] and selective clubbing of the toes with osteoarthropathy.[11]

Though these footprints of infection are quite relevant clinically, it is the bleeding, as noted, that is nearly always the central issue. An important hint to the proper diagnosis is the observation that nearly all patients, with both secondary and primary AEF, have a *sentinel* or *herald* blood loss—that is, an episode of hemorrhage that stops spontaneously. The subsequent bout of bleeding, taking place hours to days later, will predictably be massive and uncontrollable; on occasion, the premonitory hemorrhage will occur weeks or even months before the major episode. Symptomatically, hematemesis and melena are found in about

equal frequency, about 40 percent, with hematochezia in around half this many. Obviously the latter will typify the rare fistula involving lower parts of the gastrointestinal tract; aortocolic, aortosigmoid, aortoiliac and even aortoappendiceal fistulas have all been described. It is not clear why the *herald* bleed stops; it is speculated that a fall in splanchnic pressure as a physiologic response to the hemorrhage allows a small but tenuous clot to occlude the fistula. Given the pathophysiology involved, it is not surprising that major bleeding occurs subsequently.

This natural history is very characteristic and often leads to a correct clinical impression of AEF, but too often results in a false sense of security concerning the diagnostic evaluation. There is much experience reported in the literature with the usual modalities for appraising gastrointestinal hemorrhage, namely contrast studies, endoscopy and angiography. These investigations are not revealing in at least 80 percent of cases.

In the usual case, where the fistula is aortoduodenal, upper gastrointestinal studies may show a mass defect in the distal duodenum with partial obstruction. If one is fortunate, barium extravasates from the intestine and circles around the graft, giving the look of a coiled spring. At endoscopy, a pulsatile mass can be appreciated in the third portion of the duodenum and there are reports of visualization of protruding sutures or even a bile-stained prosthesis at that location. Relatively inexperienced endoscopists may interpret a duodenal mass as implying carcinoma or leiomyoma.[12]

It cannot be emphasized strongly enough that neither of these studies is sensitive in detecting AEF. Their greatest value, particularly for endoscopy, lies in excluding other causes of bleeding; it can only be regarded as good fortune to observe one of the findings noted above. One complicating fact is that patients with AEF are not immune to the other upper gastrointestinal pathologic conditions. An old autopsy study showed, for example, that peptic ulcers were three times as common in patients who had abdominal aneurysms, data which were confirmed in Kiernan's review.[6] Similarly, salicylates and alcohol are in widespread use. Therefore, endoscopists should be fastidious in identifying pathologic conditions and in assessing whether they could have accounted for the bleeding. They also should attempt to visualize the distal duodenum in all patients at risk for AEF. Truly normal endoscopic findings are compelling information pointing strongly in the direction of AEF. For fistulas to the distal parts of the gastrointestinal tract, the same principles hold; sigmoidoscopy and colonoscopy, as well as barium enema, are more useful in ruling out other causes. As for angiography, it too is seldom diagnostic. False aneurysm or a kinked graft are suggestive and contrast extravasation diagnostic of AEF but are seldom found. Mesenteric oligemia because of hemorrhage usually results in a nondiagnostic study, and the technical difficulties in carrying out angiography in this group of patients are substantial. Thus, valuable time is wasted; arteriography probably has no place in the diagnosis of most AEF.

It is conceivable that the only time an elective approach to diagnosis is warranted is in the unusual patient who presents with paraprosthetic-enteric fistula, where features of local infection dominate and where major bleeding is not imminent. An easily done test in anyone with suspected AEF is the blood culture, which if positive is quite valuable and takes little time; some believe that culturing from femoral arteries is of added benefit. Newer examinations which are expeditiously carried out include sonography and computed tomographic scanning; paraaortic mass effect or retroperitoneal fluid collection while nonspecific are circumstantially helpful. Similarly, gallium 67 scanning, though anecdotally out of favor locally, has been reported to accumulate abnormally in paraprosthetic-enteric fistulas;[13] because of the time required for reading after injection, it probably will not be of benefit in more straightforward actively bleeding AEF. One might summarize the approach to diagnosis as follows: (1) in a patient with gastrointestinal bleeding and in whom previous aortic surgical procedures have been done, AEF is the first consideration until proved otherwise and (2) endoscopy to exclude other bleeding lesions is the only obligatory test before surgical exploration.

Therapy

The operative management of primary and secondary AEF has been a source of some controversy among surgeons, but recent reviews indicate the development of a consensus. For an internist who has seen few AEF, a special problem is posed by the stable patient who has had a *herald* blood loss. It can be trying to make the leap of faith necessary to send a nonbleeding patient to the operating room for several hours of complicated,

high-mortality surgical procedures. Such patients often have multisystem disease to begin with, and indeed the primary physician may opt for supportive measures, which generally work in other causes of gastrointestinal bleeding. However, it must be recognized that the death rate of untreated AEF approaches 100 percent. Since the risk of operation is great, and exploration for an incorrect diagnosis may also prove fatal, sound clinical judgment is always required.

The operative approach to all secondary AEF should assume that the prosthetic material is infected. This requires removal of the entire graft; attempts to repair the fistula and save the prosthetic implant are nearly certain to fail. If the graft is to be removed, then assessment of the vasculature to the lower extremities must be made after aortic interruption, which is required if the graft was end-to-end. Some surgeons believe one can predict viability of the extremities in this fashion before proceeding to extra-anatomic bypass (axillofemoral and femorofemoral). However, reports of left colonic ischemia and gangrenous legs occurring postoperatively, even when the limbs appeared viable during operation, may make it prudent to proceed with bypassing save in the greatest surgical risks. If there has been a previous major leg amputation, the extra-anatomic bypass may not be required. Likewise, if the resected graft had been placed end-to-side, reestablishment of circulation through the native aorta may obviate this additional procedure.

All of this contrasts with the experience in primary AEF, where removal of the aneurysm and repair of the intestinal rent may be followed by immediate placement of an aortic prosthetic implant. The good survival data achieved with this approach[14] again indicate that infection is not usually important in the genesis of primary AEF. Though additional surgical considerations are of interest, they are beyond the scope of a medical audience, save to say that the mortality of secondary AEF treated in this way is still near 50 percent. It should not be overlooked that prevention is the best approach; given modern techniques and material, efforts made to keep more than adequate tissue or prosthetic material (or both) between graft and gut may all but eliminate this serious complication of abdominal operations.

REFERENCES

1. Brock RC: Aortic homografting. Guy Hosp Rep 102:204-228, 1953

2. Elliot JP, Smith RF, Szilagyi DE: Aortoenteric and paraprostheticenteric fistulas: Problems of diagnosis and management. Arch Surg 108:479-490, 1974

3. Kleinman LH, Towne JB, Bernhard VM: A diagnostic and therapeutic approach to aortoenteric fistulas: Clinical experience with 20 patients. Surgery 86:868-880, 1979

4. Busuttil RW, Rees W, Baker JD, et al: Pathogenesis of aortoduodenal fistula—Experimental and clinical correlates. Surgery 85:1-13, 1979

5. Rosenthal D, Deterling RA, O'Dobbell TF Jr, et al: Positive blood cultures as an aid in the diagnosis of secondary aortoenteric fistula. Arch Surg 114:1041-1044, 1979

6. Kiernan PD, Pairolero PC, Hubert JP Jr, et al: Aortic graft-enteric fistula. Mayo Clin Proc 55:731-738, 1980

7. DeWeese MS, Fry WJ: Small bowel erosion following aortic resection. JAMA 179:882-886, Mar 17, 1962

8. O'Mara AL, Imbembo C: Paraprosthetic-enteric fistula. Surgery 81:556-566, 1977

9. Reiner MA, Bran SA, Achanger G: Primary aortoduodenal fistula. Case presentation and review of the literature. Am J Gastroenterol 70:292-297, 1978

10. Gordon SL, Nicholas GG, Carter SL, et al: Aorto-enteric fistula presenting as multicentric osteomyelitis. Clin Orthop Rel Res 131:255-257, 1978

11. Stern HB, Little HA: Localized hypertrophic osteoarthropathy in the presence of an abdominal aortic prosthesis. Can Med Assoc J 118:947-948, 1978

12. Ott DJ, Kerr RM, Gelford D: Aortoduodenal fistula—An unusual endoscopic and radiographic appearance simulating leiomyoma. Gastrointest Endosc 24:296-298, 1978

13. Causey DA, Fajman WA, Perdue GD, et al: Gallium[67] scintigraphy in postoperative synthetic graft infections. Am J Radiol 134:1041-1045, 1980

14. Daugherty M, Shearer GR, Ernst CB: Primary aortoduodenal fistula: Extraanatomic reconstruction not required for successful management. Surgery 86:399-401, 1979

Important Advances in Clinical Medicine

Epitomes of Progress—Radiology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in radiology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in radiology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Radiology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Cholescintigraphy: Hepatobiliary Imaging With IDA Derivatives Labeled With Technetium 99m

A NEW GROUP of radioactive pharmaceutical agents for hepatobiliary imaging are the N-substituted iminodiacetic acid (IDA) derivatives labeled with technetium, which were first synthesized and reported in 1975. These compounds are structurally related to lidocaine and, when reacted with technetium 99m, show good extraction by the liver and rapid excretion into the bile. Several IDA derivaties (such as HIDA [dimethyl-IDA], PIPIDA [para-isopropyl-IDA] and diethyl-IDA) are now in use for diagnostic imaging.

The normal time sequence of an IDA scan depends somewhat on the specific product used but may be generalized as follows: After intravenous injection of 5 to 10 mCi of the agent in a human who has fasted for 2 to 12 hours, an immediate *blood-pool phase* is seen during the first 30 to 60 seconds. By three to five minutes blood clearance is almost complete and the *early hepatic parenchymal phase* has peaked. The *renal excretory phase* occurs from about 15 to 30 minutes after injection. *Bile ducts* are seen best from about 10 to 20 minutes after injection, and the descending portion of the *duodenum* may be seen from about 20 to 30 minutes. The *gallbladder phase* occurs from 13 to 60 minutes postinjection in adequately fasted, normal patients; however, if the patient has *not* fasted before examination, gallbladder exclusion has been described and may result in a falsely abnormal study. A routine study includes views of the liver and biliary tree area at 1, 5, 15, 30, 45 and 60 minutes. Computer acquisition and processing of images are not usually necessary, unless gallbladder emptying in response to cholecystokinin is to be studied. If an abnormal result is apparent within the first hour, it may be necessary to continue intermittent imaging for two to five hours following injection and, possibly, a 24-hour delayed view may help to detect presence of any bowel activity.

Clinical indications for hepatobiliary imaging include the following: (1) The differential diagnosis of obstructive jaundice; (2) diagnosis of biliary atresia in infants; (3) evaluation of biliary drainage pathways and intestinal bile flow postoperatively and determining the presence of biliary reflux; (4) assessment of hepatobiliary structure and function in cold areas on the technetium 99m sulfur colloid (liver and spleen) scan, and (5) determination of cystic-duct patency in cases of suspected acute cholecystitis.

The success of the IDA derivatives in the dif-

ferential diagnosis of obstructive jaundice depends on the degree of hyperbilirubinemia. With HIDA and PIPIDA, adequate visualization of the hepatic parenchyma and biliary tract structures has been reported with serum bilirubin levels of up to 5 to 8 mg per dl; higher bilirubin levels have produced variable and unpredictable results. The newer agents have shown potential for demonstrating biliary ducts at much higher bilirubin levels and may prove superior in further investigation of jaundice. Scintigraphic diagnosis of infant biliary atresia may also relate to the bilirubin level and the age of the patient at the time of examination. Infants with atresia studied before 3 months of age have been reported to show good hepatocyte clearance but no bile flow into the bowel; older infants showed poor hepatocyte clearance as well as no bile flow. In newborns with hepatitis, variable degrees of hepatocyte clearance were seen, but intestinal activity was usually demonstrated.

In acute complete extrahepatic obstruction, where hepatocellular function is still relatively intact, the study may show the following: abrupt cutoff of activity at the level of obstruction; dilated bile ducts; retention of the radioactive pharmaceutical agent in the liver and hepatic ducts, with no excretion into the common bile duct or duodenum, or prolonged retention and *no* ductal visualization. With a patent cystic duct, the gallbladder will be visualized and may show intense accumulation of activity over time, because the agent cannot exit into the bowel.

Hepatobiliary imaging of bile flow patterns and bile duct anatomy has also been found useful in evaluating congenital, postoperative or posttraumatic abnormalities. The cholescintiscan can demonstrate the caliber and functional patency of an anastomosis; define the preferential route of bile flow as well as the rate of flow; detect bile leakage and assess its extent and course, and visualize cystic duct remnants. Scintiscans have also been found useful in evaluating the response to medical or surgical treatment; in detecting bile leaks secondary to traumatic disruption of the biliary tract, and in diagnosing congenital cystic dilatation of the biliary tree, involving either the intra- or extrahepatic ducts.

The most widely accepted application of cholescintigraphy, however, is in the differential diagnosis of acute cholecystitis. The procedure has a reported 95 percent sensitivity, 100 percent specificity, and 98 percent accuracy for detecting cystic-duct obstruction in patients with acute abdominal pain.

KATHRYN F. WITZTUM, MD

REFERENCES

Wistow BW, Subramanian G, Heertum RL, et al: An evaluation of ^{99m}Tc-labeled hepatobiliary agents. J Nucl Med 18:455-461, May 1977

Rosenthall L, Shaffer EA, Lisbona R, et al: Diagnosis of hepatobiliary disease by ^{99m}Tc-HIDA cholescintigraphy. Radiology 126:467-474, Feb 1978

Weissman HS, Frank M, Rosenblatt R, et al: Cholescintigraphy, ultrasonography and computerized tomography in the evaluation of biliary tract disorders. Semin Nucl Med 9:22-35, Jan 1979

Rosenthall L, Fonseca C, Arzoumanian A, et al: ^{99m}Tc-IDA hepatobiliary imaging following upper abdominal surgery. Radiology 130:735-739, Mar 1979

CT Evaluation of Lymphoma

ABDOMINAL AND PELVIC computed tomography (CT) is being used with increasing frequency in the initial evaluation of patients with Hodgkin disease (HD) and non-Hodgkin lymphoma (NHL). Data regarding the accuracy of this technique in assessing subdiaphragmatic disease indicate distinct advantages compared with other imaging techniques and a few disadvantages. Information derived from surgical staging procedures remains superior, but there is a growing trend toward selectively replacing operative techniques.

Spleen and liver. CT provides relatively accurate correlative data on organ size; however, spleen and liver size bears little correlation to absence or presence of disease, unless these organs are substantially enlarged, a condition usually recognized by palpation. Occasionally, defects of lower attenuation coefficient are seen which correlate with tumorous nodules. Usually, however, tumor involvement of these organs is manifested as nodules smaller than 1 cm, which is beyond the resolving ability of CT scanners at present.

Retroperitoneal and pelvic lymph nodes. Lymphography is more accurate than CT in evaluating those lymph nodes which are opacified because it permits evaluation of derangements of architecture in normal or minimally enlarged nodes. However, CT visualizes other node groups (such as celiac axis, splenic hilum, porta hepatis) and can demonstrate disease when these nodes become enlarged.

Mesenteric nodes. These nodes, involved in greater than 55 percent of NHL, are usually bulky and readily seen with CT. Conversely, involvement is present in less than 4 percent of HD and, often, these involved nodes are normal in size. Thus, CT is useful in evaluating patients with NHL but not HD for mesenteric lymphadenopathy.

Bone and bone marrow. Percutaneous bone

marrow biopsy is the procedure of choice to evaluate the marrow. With *bone* involvement, CT more clearly defines the extent of extraosseous disease compared with bone radiography and nuclear medicine scans.

CT provides excellent information regarding the anatomic extent of bulky disease, which is often important in treatment planning. Evaluation of patients after treatment with follow-up CT scans provides reliable evidence of response to treatment and evaluation of those in whom relapse of disease is suspected.

RONALD A. CASTELLINO, MD

REFERENCES

Breiman RS, Castellino RA, Harell GS, et al: CT-pathologic correlations in Hodgkin's disease and non-Hodgkin's lymphoma. Radiology 126:159-166, Jan 1978

Best JJK, Blackledge G, Forbes W, et al: Computed tomography of abdomen in staging and clinical management of lymphoma. Br Med J 2:1675-1677, Dec 16, 1978

CT Evaluation of Pulmonary Metastatic Disease

COMPUTED TOMOGRAPHY (CT) is capable of showing pulmonary nodules invisible on plain radiographs and standard whole lung tomograms. Therefore, CT has been used extensively for the diagnosis of pulmonary metastatic disease.

In general, nodules 3 mm to 6 mm in diameter can be seen with CT, while only those greater than 6 mm in diameter are visible using conventional tomography. In several series of patients with metastatic pulmonary nodules, CT showed more nodules than conventional tomography in a third to a half of patients.

Although its absolute spatial resolution is less than that of plain radiographs, CT's superior density resolution and the absence of overlying structures (as on plain films) or tomographic blur (as on conventional tomograms) enhances the detectability of lung nodules.

The cross-sectional image format of CT is also helpful in showing lung metastatic lesions. In pathological studies, it has been shown that a large percentage of metastatic deposits within the lung are subpleural. These lesions are difficult to see using conventional radiographic studies unless projected in tangent; this is not the case when using CT. Similarly, lesions near the hila or mediastinum as well as those located deep within a costophrenic sulcus may be missed using plain films and tomograms but are usually easily seen with CT.

In patients with suspected metastatic tumors, the detection of additional nodules using CT can affect treatment. In some patients, CT shows lung nodules when findings on plain radiographs and conventional tomograms appear normal; this is of obvious importance for the prompt institution of appropriate treatment. Also, in patients with lung nodules visible using standard techniques, CT may show additional nodules—information of value to the surgeon if excision of metastatic nodules is planned. Lastly, CT may show evidence of extrapulmonary (mediastinal or abdominal) metastatic lesions that would alter the therapeutic approach.

It must be emphasized, however, that not all pulmonary nodules seen in patients with a malignant tumor are metastatic deposits; some represent granulomas or normal subpleural lymph nodes. The smaller the nodule, the less likely it is to be a metastatic deposit regardless of the technique used to detect it. In one study, 60 percent of nodules detected by CT and not by conventional tomograms were not metastatic tumors; in other series, this percentage was lower. Although the frequency of such false-positive nodules detected by CT varies, it is clear that care must be taken in the diagnosis of pulmonary metastatic disease in patients with only one or two small nodules.

W. RICHARD WEBB, MD

REFERENCES

Schaner EG, Shang AE, Doppman JL, et al: Comparison of computed and conventional whole lung tomography in detecting pulmonary nodules: A prospective radiologic-pathologic study. Am J Roentgenol 131:51-54, Jul 1978

Muhm JR, Brown LR, Crowe JK, et al: Comparison of whole lung tomography and computed tomography for detecting pulmonary nodules. Am J Roentgenol 131:981-984, Dec 1978

Mintzer RA, Malave SR, Neiman HL, et al: Computed vs. conventional tomography in evaluation of primary and secondary pulmonary neoplasms. Radiology 132:653-659, Sep 1979

Ultrasound Scanning in Gallbladder Disease

RECENT TECHNICAL ADVANCES in high-resolution real-time ultrasound scanners have greatly improved the speed and accuracy of diagnosis in gallbladder disease. Real-time sector scanners avoid most of the technical difficulties associated with conventional articulated-arm static scanners. As opposed to a cholecystogram (with orally given contrast medium), an ultrasound evaluation is not hampered by hepatic, biliary or gastrointestinal dysfunction. When carried out by an experienced ultrasonographer, the real-time technique is the examination of choice in patients with suspected gallbladder disease.

Real-time ultrasound scanning of the gallbladder has a sensitivity of 98 percent and a specificity

of 95 percent for the diagnosis of cholelithiasis. Stones as small as 1 to 2 mm can be identified as shadowing echogenic foci within the gallbladder. Single, small gallstones within the gallbladder neck are the ones most often missed. Cholelithiasis does not, however, always infer acute cholecystitis and must be evaluated in view of the clinical history or confirmed by a biliary isotope scan.

Other types of gallbladder disease are easily evaluated by real-time ultrasonography. Pericholecystic fluid collections are easily identified and can serve as further evidence for acute cholecystitis in the proper clinical setting. Focal thickening of the gallbladder wall as seen with polyps or adenomyosis can be visualized. Diffuse thickening of the wall, though seen commonly in acute or chronic cholecystitis, is a nonspecific finding also associated with hypoalbuminemia and acute viral hepatitis.

Because a real-time ultrasound examination is equal in accuracy to a cholecystogram for the detection of gallstones, is independent of function, images all the organs surrounding the gallbladder and can detect abnormalities of the gallbladder wall, it should be considered our most versatile modality for gallbladder evaluation.

CHARLES E. FISKE, MD
ROY A. FILLY, MD

REFERENCES

Cooperberg PL, Burhenne HJ: Real-time ultrasonography: Diagnostic technique of choice in calculous gallbladder disease. N Engl J Med 302:1277-1279, Jun 5, 1980

Wolson AH, Goldberg BB: Gray-scale ultrasonic cholecystography. A primary screening procedure. JAMA 240:2073-2075, Nov 3, 1978

Leopold GR, Amberg J, Gosink BB, et al: Gray scale ultrasonic cholecystography: A comparison with conventional radiographic techniques. Radiology 121:445-448, Nov 1976

Therapeutic Angiography

REFINEMENTS in angiographic technique and catheter technology have resulted in two important developments, percutaneous transcatheter embolic occlusion of vessels and transluminal angioplasty with percutaneous vascular dilatation.

Percutaneous vascular embolic occlusion was first used by Rösch in the treatment of upper gastrointestinal hemorrhage. The technique is now widely used in the nonsurgical obliteration of arteriovenous malformations of the head, neck, extremities and internal organs. It also is used in the treatment of splenic artery aneurysms; as a means of reducing tumor vascularity preoperatively, and for transhepatic obliteration of esophageal varices. It is under investigation for treatment of varicoceles.

Multiple embolic agents are used in this technique, including autologous blood clot, liquid silicone and particulate agents such as gelfoam, polyvinyl alcohol (Ivalon) and microspheres. All of these agents except autologous clot and gelfoam produce permanent occlusion. Mechanical devices are also used for permanent occlusion. Among these are Gianturco-Wallace-Anderson coils, detachable balloons, bristle brushes and expandable polyvinyl alcohol plugs. The mechanical devices offer an advantage over particulate agents because they avoid the risk of reflux of particles to other organs or the extremities.

In many cases, they are used in combination. The particulate agent initially occludes central small vessels and the mechanical device then occludes the larger feeding vessels. Most of these agents are commercially available while a few (such as cyanoacrylate glue) remain investigational.

Percutaneous vascular dilatation techniques were first shown to be feasible by Dotter, who used coaxial Teflon catheters for gradual dilatation. Today, transluminal angioplasty is done using Grüntzig balloon catheters, which are available with various balloon sizes. Proper selection of balloon size permits dilatation of arteries of varying caliber.

The technique has been successful with good long-term results in the dilatation of iliac, femoral and popliteal artery stenoses and in aortic dilatation. Recently it has been used in renal artery stenosis as an alternative to operating in the treatment of renovascular hypertension. It is also under investigation for dilatation of coronary artery stenosis or stenotic saphenous vein bypass grafts in selected patients.

ANTOINETTE S. GOMES, MD

REFERENCES

Grace DM, Pitt DF, Gold RE: Vascular embolization and occlusion by angiographic techniques as an aid or alternative to operation. Surg Gynecol Obstet 143:469-482, Sep 1976

Zeitler E, Grüntzig A, Schoop W: Percutaneous Vascular Recanalization: Technique, Application, Clinical Results. Berlin, Heidelberg, New York, Springer-Verlag, 1978

Mammography: Who Needs a Mammogram?

MAMMOGRAPHY is the most accurate noninvasive means of detecting breast carcinoma, especially very small lesions that are most amenable to cure.

Diagnostic mammography involves a one-time evaluation of patients with signs or symptoms that suggest the possibility of breast cancer. Specific indications include palpable mass, nipple dis-

charge, skin or nipple retraction, focal skin thickening, nipple abnormalities suggesting Paget disease, unexplained axillary adenopathy and search for primary tumor site in women with documented metastasis. In these clinical settings, mammography can be very helpful in deciding whether and when biopsy should be done, in defining the extent of breast cancer if present and in evaluating asymptomatic areas in the ipsilateral and contralateral breast for clinically occult cancer. Clearly, diagnostic mammography is a high-yield procedure with substantial clinical benefit. Because only one examination is necessary, the radiation dose is very low and the carcinogenic risk is minimal. Because benefit exceeds risk by such a large margin, mammography is considered an essential part of the diagnostic evaluation of all symptomatic patients 30 years old and older.

Screening mammography involves repeated examination of totally asymptomatic patients. In this setting, mammography is instrumental in detecting many small lesions that otherwise would grow much larger and possibly become more widespread before the onset of clinical symptoms. The benefits of screening mammography do not exceed the presumed risk to the same degree as in diagnostic examinations because the yield of cancer is considerably lower in asymptomatic patients (reduced benefit) and because multiple examinations are needed, resulting in higher cumulative radiation dose (increased risk). Because neither benefit nor risk can be quantified precisely, there is disagreement over the proper role of screening mammography. However, it is generally accepted that because the risk of radiation-induced cancer is directly proportional to radiation dose, any reduction in dose is accompanied by a parallel decrease in risk. Therefore, the recent dose reductions for both xeromammography (0.4 to 1.0 rad breast tissue dose per examination) and screen-film mammography (0.05 to 0.15 rad per examination) make these techniques much more attractive now than several years ago. Fortunately, a consensus now exists, arguing for yearly screening mammography for the following: (1) all women over the age of 50, (2) women from the ages of 35 to 50 who are at high risk for the development of breast cancer (for example, breast cancer in a first-degree relative or a previous breast biopsy specimen that showed a premalignant lesion) and (3) all women in whom cancer has already developed in one breast, regardless of age, provided that there is no evidence of (incurable) metastatic disease. There is also widespread agreement that all women between 35 and 40 should have a single mammography examination to serve as a baseline for future comparison.

EDWARD A. SICKLES, MD

REFERENCES

National Institutes of Health/National Cancer Institute Consensus Development Meeting on Breast Cancer Screening: Issues and Recommendations. J Natl Cancer Inst 60:1519-1521, Jun 1978

Moskowitz M: Mammography in medical practice—A rational approach. JAMA 240:1898-1899, Oct 20, 1978

Sickles EA: Xeromammography versus screen-film mammography: Pros and cons of the two techniques (Information). West J Med 134:273-274, Mar 1981

Eddy D: American Cancer Society report on the cancer-related health check-up: Cancer of the breast. CA 30:224-229, Jul-Aug 1980

Applications of CT Scanning in Orthopedics

COMPUTERIZED TOMOGRAPHY (CT), originally introduced into clinical medicine for use in neuroradiology, now has been refined and adapted for scanning all parts of the body. Applications of CT in orthopedic radiology are under investigation.

In July 1978 the first article reporting the technique of CT investigation of the musculoskeletal system appeared in the *Journal of Bone and Joint Surgery*. This article stressed the value of CT scanning in the assessment of musculoskeletal tumors. The most obvious advantage to orthopedic surgeons lies in the unique ability of CT to clearly define the size and extent of soft tissue tumor masses before surgical treatment. The limits of bony involvement in malignant conditions also are assessed more accurately by CT than by conventional roentgenology, particularly with respect to extent of tumor in the medullary space.

CT scanning in skeletal trauma is not widespread. In most routine cases CT has no advantage over conventional radiography and may delay treatment because of the longer imaging time. However, in complicated pelvic and hip fractures, CT provides a picture of the relationship of fracture fragments far superior to that possible with conventional tomography. CT can show previously unsuspected acetabular fractures and intra-articular bony fragments in hip fractures.

In spinal examinations, CT is an adjunct procedure which can better define abnormal anatomy that has been identified using simpler methods such as plain films. CT will show the relationship of the vertebral body and posterior elements to the spinal canal and possible encroachment on the

canal by bony fragments after spine trauma. Similarly, the relationship of inflammatory and tumor masses to the spinal canal can be evaluated better by CT than by conventional methods and the introduction of metrizamide may extend the diagnostic applications of computerized tomography in the spine.

The major limitations of spinal CT are related to the technique of examination. Scout view, tilting gantry and perhaps multiplanar reconstruction capabilities are necessary to diagnose subtle changes in degenerative disc and facet disease. Fourth generation machines with high-resolution capabilities are producing images with excellent anatomic detail within the spinal canal. Unfortunately, however, these are not generally available so that widespread application of CT diagnosis in these problems may be delayed.

LAWRENCE W. BASSETT, MD
ANTHONY A. MANCUSO, MD

REFERENCES

Schumacher TM, Genant HK, Korobkin M, et al: Computed tomography. Its use in space-occupying lesions of the musculoskeletal system. J Bone Joint Surg 60:600-607, Jul 1978

Lasda NA, Levinsohn EM, Yuan HA: Computerized tomography in disorders of the hip. J Bone Joint Surg 60:1099-1102, Dec 1978

Roub LW, Drayer BP: Spinal computed tomography: Limitations and applications. Am J Roentgenol 133:267-273, Aug 1979

Thallium 201 Myocardial Imaging

THALLIUM 201 myocardial perfusion imaging has become a widely used noninvasive technique for differentiating normal, reversibly ischemic and irreversibly infarcted myocardial tissue. The thallous ion is thought to function as a potassium analog, and cellular uptake of the tracer therefore requires not only adequate regional myocardial perfusion, but also is dependent on the functional integrity of the sodium-potassium adenosine triphosphatase-activated pump, fueled with glucose by aerobic metabolism. Thus, in patients with coronary artery disease, areas of infarction or local tissue ischemia, or both, will show reduced thallium uptake and will appear as cold defects on scintigrams.

Because myocardial perfusion in the distribution of coronary arteries with high-grade stenoses may be essentially normal at rest, it has become customary to do thallium 201 scintigraphy in conjunction with exercise stress testing. Treadmill exercise is most commonly employed, although upright or supine bicycle stress has been used successfully. Regardless of the exercise technique employed, it is of paramount importance that the patient be brought to a true maximum, symptom-limited end point to achieve the highest possible heart rate and blood pressure measurement that is safe for the patient. Acceptable end points for stress scintigraphy include typical anginal chest pain, 2 mm or more flat or down-sloping ST segment depression of at least 0.08 seconds duration, severe fatigue, dyspnea or claudication. The importance of reaching maximal stress cannot be emphasized too strongly; it has, in fact, been shown that only 53 percent of the thallium perfusion defects detected after maximal exercise could be visualized after submaximal exercise.

A typical study protocol is as follows: The patient is connected to a routine twelve-lead electrocardiograph and an indwelling intravenous catheter is inserted into the arm. Graded levels of exercise are performed until fatigue or symptoms appear. The radioactive pharmaceutical agent is injected through the previously inserted intravenous catheter at the point of peak stress and exercise is continued for approximately 45 to 60 seconds to allow for initial thallium distribution. Following termination of exercise, a final multiple-lead electrocardiogram (ECG) is obtained, and the chest leads are then immediately removed to allow prompt commencement of imaging within less than three minutes after exercise. Continued ECG monitoring is maintained by the modified limb leads. It is important to obtain the initial image as early as possible because occasionally a stress-induced defect will "fill in" as early as 10 minutes following exercise. Myocardial perfusion defects (cold spots) seen on the immediate post-stress images may be due either to reversible, stress-induced ischemia or to previous myocardial infarction which has resulted in scar. To distinguish between these entities, delayed or redistribution images are obtained three to six hours after the initial scintigrams. Defects on the immediate poststress images that show no significant change on the delayed redistribution views are assumed to represent scar. Conversely, defects present on the immediate poststress scintigrams that are normal on the delayed images indicate stress-induced, reversible ischemia.

Resting thallium 201 scintigrams have also been shown to be extremely sensitive for the diagnosis of acute myocardial infarction, with sensitivity approaching 100 percent within the first 6 to 12 hours after the onset of symptoms, at a time when the ECG or enzymes may not yet be diagnostic.

While this technique cannot, in general, distinguish acute from old myocardial infarction, it can be very useful in making the diagnosis of noncardiac chest pain in a patient with symptoms suggestive of acute myocardial infarction.

Thallium scintigraphy has also been found useful in the assessment of a coronary artery stenosis visualized on coronary angiography but which may be of equivocal hemodynamic significance. In this setting, a stress-induced reversible defect in the distribution of the artery in question is certain evidence that the lesion is physiologically significant. While a negative test finding does not rule out physiological significance of a coronary lesion, it does decrease the likelihood that significant stress-induced ischemia is occurring with similar levels of stress.

Many experts believe that thallium 201 scintigrams are among the most difficult images in nuclear medicine to interpret competently and consistently. Thus, this procedure is recommended only at those centers where suitable instrumentation and experienced practitioners allow for the strictest standards of quality control.

KENNETH GERBER, MD

REFERENCES

Pohost GM, Alpert NM, Ingwell JS, et al: Thallium redistribution: Mechanisms and clinical utility. Semin Nucl Med 10:70-93, Jan 1980

Pierson RN Jr, Friedman MI, Tansey WA, et al: Cardiovascular nuclear medicine: An overview. Semin Nucl Med 9:224-240, Oct 1979

Botvinick EH, Dunn RF, Hattner RS, et al: A consideration of factors affecting the diagnostic accuracy of thallium-201 myocardial perfusion scintigraphy in detecting coronary artery disease. Semin Nucl Med 10:157-167, Apr 1980

Hamilton GW: Myocardial imaging with thallium-201: The controversy over its clinical usefulness in ischemic heart disease. J Nucl Med 20:1201-1205, Nov 1979

Computed Tomography of the Spine and Spinal Contents

RECENT DEVELOPMENTS in computed tomography (CT) have made it possible to carry out consistent diagnostic spinal CT. The current CT scanners allow for accurate localization of the level of section by a cursor with appropriate gantry angulation for the area under study. For example, in evaluating the intervertebral disc spaces, it is possible to angle the gantry through the interspace without including adjacent bony structures. Gantry angulation is also of value in obtaining scans of areas of previous operations or trauma without metallic or other high-density hardware.

Third and fourth generation scanners obtain greater detail within the bony spinal canal. Thinner sections with increased spatial and density resolution produce images with increased anatomic detail. Thin sections (1.5 mm or less) are used to define small nerve roots, vessels and ligaments in the spinal canal.

While newer body scanners produce images in 10 seconds or less, the maximum surface dose per slice is approximately 5 to 7 rads, depending on the technical factors. The dose for a series of scans abutting each other increases by about 20 percent.

Of equal importance to the equipment advances is the introduction of metrizamide (Amipaque) for carrying out conventional myelography. This nonionic water-soluble contrast medium has extended the application of spinal CT scanning to allow consistent documentation of the spinal subarachnoid space and the spinal cord. A metrizamide myelogram alone may be inadequate or equivocal; however, a diagnostic CT scan can be done up to four hours after the myelogram.

The Society for Computed Body Tomography has reviewed the indications for spinal CT, dividing them into three types. Type I examinations (no contrast medium) are done in cases of suspected disc herniation, facet joint hypertrophy or spinal stenosis. Unenhanced CT is useful for identifying fractures or for localization for CT-guided biopsy or aspiration procedures. Conventional spinal CT is an ideal alternative to myelography in patients who may have allergy to contrast agents or who may have arachnoiditis.

Type II examinations use diluted intrathecal metrizamide (5 to 7 ml of 190 mg iodine per ml), while type III examinations use concentrated metrizamide injected for conventional myelography followed by CT. Type II and type III examinations are indicated for patients with congenital dysraphic abnormalities, including cases of overt meningoceles or meningomyeloceles or cases of occult dysraphism in which there may be a fatty tumor or intraspinal meningocele tethering the spinal cord. The intraspinal component of lesions can be identified with great precision by metrizamide-enhanced spinal CT. Cases with bone destruction or erosion also can be well examined by CT. The full extent of masses can thus be defined simultaneously whenever the lesions are both intra- and extraspinal.

In cases of cord atrophy or cord expansion, conventional myelography may not precisely define the size of the cord. However, metrizamide-enhanced spinal CT will clearly show and measure

the degree of atrophy or enlargement. At the level of the foramen magnum, intraspinal masses or masses extending intracranially are best examined by metrizamide-enhanced CT.

Finally, CT permits evaluating results of surgical operations as well as changes occurring in the spinal canal. In patients receiving radiation therapy, CT is used to define the treatment ports and to document the results of irradiation.

ANTON N. HASSO, MD
P. E. BILLIMORIA, MD

REFERENCES

Alfidi RJ, Evens RG, Glenn W, et al: Special report: New indications for computed body tomography. Am J Roentgenol 133:115-119, Jul 1979

Haughton VM, Syvertsen A, Williams AL: Soft-tissue anatomy within the spinal canal as seen on computed tomography. Radiology 134:649-655, Mar 1980

Metrizamide Myelography

IN THE SHORT TIME that metrizamide (Amipaque) has been available in this country, it has greatly changed how myelography is done. This highly versatile agent may be used with conventional filming, tomography, or computed tomography (CT) to give diagnostic information which was not readily available with isophendylate (Pantopaque).

The advantages of metrizamide stem from its physical properties. Being water-soluble, it will penetrate narrow spaces and, thus, is a better agent for outlining nerve root sleeves and spaces about tumors and for showing the spinal cord near sites of compression. The necessity of mixing the contrast agent with its diluent immediately before myelography appears inconvenient, but is advantageous in allowing the operator to tailor the concentration precisely to the desired study. The gravitational layering effect works well to fill dependent nerve root sleeves early in the study while the mixing of metrizamide with cerebrospinal fluid, which results from patient motion, can be used to outline the spinal cord in later phases of the study. Because the contrast agent need not be withdrawn, it may be injected into areas from which withdrawal would be impossible, such as in the spinal canal above a thoracic block. Arachnoiditis following the use of metrizamide is virtually unknown; therefore, this contrast agent may be used in situations in which one would hesitate to use isophendylate, such as in cases of trauma and suspected arachnoiditis.

Metrizamide also has its disadvantages. The myelography must be planned in such a way that the contrast agent is moved gently from one region to another, avoiding excessive mixing that can rapidly dilute the agent to the point of being barely visible. Also, it may be difficult to examine the entire spinal canal without using large amounts of relatively high concentration, which increases the chances of side effects. Headache and nausea seem to be more prevalent after metrizamide myelography than after isophendylate myelography. Confusional states sometimes occur in older patients following metrizamide myelography, and coma has occurred in a few cases. The incidence of seizures shortly after myelography, originally reported to be much less than 1 in 1,000 in the European experience, is higher in the United States. This difference is probably related to the prior use in this country of isophendylate with its relatively low immediate toxicity, while European and Scandinavian myelographers were accustomed to working with aqueous contrast agents of higher toxicity, thereby developing more conservative myelographic techniques.

The combination of metrizamide and CT makes it possible to examine difficult areas using relatively low amounts and concentrations of the contrast agent, thereby decreasing the side effects Areas where this technique is particularly helpful include the foramen magnum, cisterns about the brain stem and the suprasellar region, and investigation of syringomyelia. CT may also be used to salvage a myelographic study of the spinal canal in which the metrizamide has become too dilute for conventional filming.

Though not a perfect contrast agent, metrizamide is highly versatile and represents a significant advance over earlier myelographic contrast agents.

JOHN R. BENTSON, MD

REFERENCES

Ahlgren P: Amipaque myelography without late adhesive arachnoid changes. Neuroradiology 14:231-233, Feb 17, 1978

Baker RA, Hillman BJ, McLennan JE, et al: Sequelae of metrizamide myelography in 200 examinations. Am J Roentgenol 130:499-502, Mar 1978

Skalpe IO: Adhesive arachnoiditis following lumbar radiculography with water-soluble contrast agents. A clinical report with special reference to metrizamide. Radiology 121:647-651, Dec 1976

Percutaneous Transhepatic Biliary Drainage

ALTHOUGH percutaneous transhepatic biliary drainage has been used for the past decade, its use has been greatly increased since angiographic catheterization techniques were applied by Ring and co-workers. These involve placement of cathe-

ters either proximal to lesions, permitting external drainage or across lesions, into the duodenum, permitting internal drainage.

Following administration of antibiotics and sedation, a fine-needle transhepatic cholangiogram is done on all patients prior to the placement of a percutaneous drainage catheter. This allows confirmation of the diagnosis of biliary obstruction, demonstrates the anatomy of the bile ducts and may demonstrate the site and nature of the obstructing lesion. A 16-gauge sheathed needle is then introduced from the right midaxillary line using the opacified biliary tree as a guide. When an appropriate duct is cannulated, the metal stylet is removed and the Teflon sheath is slowly withdrawn until bile flow is established. Once bile flow is established, an angiographic guidewire is introduced. The sheath-guidewire combination is then manipulated distally to the site of the obstruction. If the obstruction is crossed, the guidewire is manipulated into the duodenum and, using several intermediate steps, a 7-French or 8-French pigtail catheter is introduced with holes above and below the lesion. This permits either external or internal bile drainage. If the guidewire cannot be manipulated past the lesion, a pigtail catheter is introduced and external drainage begun.

This procedure is used preoperatively in patients with malignant obstruction to allow the patient to be completely evaluated and optimal presurgical physiologic status to be attained. Alternatively, those patients who are not surgical candidates may be effectively palliated. Patients with biliary strictures, obstructing calculi, obstructing pancreatitis and postoperative problems, have also benefited from temporary percutaneous drainage while awaiting more definitive therapy.

The success rate in placing a catheter in an obstructed biliary tree is approximately 90 percent. Of these patients, internal drainage can be established in about 85 percent. The most common complication is sepsis. In short-term drainage in patients without antecedent infection, the rate of cholangitis is 4 percent to 15 percent. However, this can usually be treated with fluids, antibiotic drugs and external drainage. The incidence of cholangitis in patients with chronic drainage is higher; however, this is usually due to blockage of the catheter and can be readily treated by medical management and replacement of the obstructed tube. Bleeding, leakage of bile and pneumothorax have also been reported; however, these are infrequent complications and have not required emergency operations.

Because of low morbidity and its ability to aid significantly in the management of difficult problems in the obstructed biliary tree, percutaneous biliary drainage is rapidly becoming an important adjunct in the management of surgical jaundice.

HARVEY ROSENKRANTZ, MD

REFERENCES

Ferrucci JT Jr, Mueller PR, Harbin WP: Percutaneous transhepatic biliary drainage. Technique, results, and applications. Radiology 135:1-13, Apr 1980

Hansson JA, Hoevels J, Simert G, et al: Clinical aspects of nonsurgical percutaneous transhepatic bile drainage in obstructive lesions of the extrahepatic bile ducts. Ann Surg 189:58-61, Jan 1979

Pollock TW, Ring ER, Oleaga JA, et al: Percutaneous decompression of benign and malignant biliary obstruction. Arch Surg 114:148-151, Feb 1979

Ring EJ, Oleaga JA, Freiman DB, et al: Therapeutic applications of catheter cholangiography. Radiology 138:333-338, Aug 1978

Contemporary Treatment for Early Breast Cancer

THE WIDE EXPOSURE that the topic of breast cancer has received in the media has helped to prompt women to explore alternate methods to mastectomy. Further, it is now a law in California that when mastectomy is proposed to a patient, alternate methods of treatment must be discussed. This trend away from mastectomies suggests that results from conservative approaches to treatment can no longer be dismissed as preliminary and, in fact, mastectomy for early breast cancer may soon be outdated. Lumpectomy plus radiation therapy has been used long enough and on sufficient numbers of patients to be conclusive as one such approach.

Prosnitz, from Yale, recently presented data on 293 patients treated at four East Coast university hospitals. Patients had stage I and II disease and were treated with local excision and radiation therapy. Five- and ten-year survival rates were comparable with those of the mastectomy series, and the local control rate was 92 percent. Of the 8 percent that failed locally, half had no evidence of disease after salvage operations. Cosmetic results were good to excellent in 85 percent of patients.

Peters, from Princess Margaret Hospital in Toronto, reported on 203 patients with early breast cancer who were treated with limited surgical procedures and radiation therapy; 609 matched patients who had received mastectomies

were used as controls. In 2- to 30-year follow-up studies, no significant differences in survival rates were noted.

Bonadonna recently reported the five-year results of a study in Milan where a randomized trial is underway. This trial compares the results of segmental mastectomy followed by radiation therapy, with those of Halsted radical mastectomy. Patients had T1, N0 and M0 lesions. By May 1980 more than 700 patients had been included. Relapse-free survival was 83 percent for the conservative group. Total survival was 89.7 percent and 88.5 percent, respectively. This study is exciting because it is both prospective and randomized.

As public interest in alternate methods to mastectomy for treatment of early breast cancer grows, physicians need to be aware of such options.

JEROME STUHLBARG, MD
THOMAS G. SIMKO, MD
KENNETH M. TOKITA, MD

REFERENCES

Prosnitz LR, Goldenberg IS, Harris J, et al: Primary radiotherapy for stage I and II breast cancer: Follow up report from four East Coast university hospitals. Int J Radiat Oncol Biol Phys 6:1339-1340, Oct 1980

Peters MV: Wedge resection with or without radiation in early breast cancer. Int J Radiat Oncol Biol Phys 2:1151-1156, Nov-Dec 1977

ADVISORY PANEL TO THE SECTION ON RADIOLOGY

GABRIEL H. WILSON, MD
Advisory Panel Chairman
Section Editor
CMA Scientific Board Representative
University of California, Los Angeles

JOSEPH SCALLON, MD
CMA Section Chairman
Torrance

S. WALTER KRAN, MD
CMA Section Secretary
San Leandro

MICHAEL A. LOPIANO, MD
CMA Section Assistant Secretary
Ventura

LEON KASEFF, MD
Immediate Past Panel Chairman
Burlingame

ANTON N. HASSO, MD
Loma Linda University

RONALD CASTELLINO, MD
Stanford University

C. JOHN ROSENQUIST, MD
University of California, Davis

RICHARD M. FRIEDENBERG, MD
University of California, Irvine

ROBERT N. BERK, MD
University of California, San Diego

A. R. MARGULIS, MD
University of California, San Francisco

JAMES HALLS, MD
University of Southern California
Los Angeles

WILLIAM JOHNSON, MD
Burlingame

EDITORIALS

Of Gerontology, Geriatrics and Gereology

THE AVERAGE life expectancy at birth has been steadily increasing, as is well known. Medical science and better health care have played their parts at each stage of human life, as have improved sanitation, better nutrition, power-assisted human labor and much else. The human population at any given moment is the aggregate of the individual lives that are moving inexorably through a continuum of stages starting from conception in a mother's womb. In recent years both ends of the normal human life span have received special attention, and health care and quality of life, particularly in the later years, are becoming of increasing economic and humanitarian importance.

Shakespeare succinctly described seven stages of life. For our purposes, perhaps we can be satisfied with three. There is a period of growth and development before the prime of life. This is a time of physical and mental maturation and of steadily diminishing dependence on others. Then there is the prime of life, a time of maximum vigor and productivity and of minimal dependence on others. Then, if one lives long enough, there is eventually a third period beyond the prime, when vigor lessens and dependence on others usually increases. At both ends of the life span there is an unavoidable need for the help and support of those who are in the prime of life. As the number of persons living on into the later decades and past their prime increases, more attention is being given to the processes of aging, to the ailments that mar health and the quality of life for older persons, and to the social, economic and political consequences of a growing population who have returned to dependency on others. It is suggested that *gerontology* is the study of the processes of aging, that *geriatrics* is concerned with the ailments that accompany growing older, and that *gereology* be used for the study of the social, economic and political consequences of a growing population who have passed their prime.

There is much to be done in each of these fields and there is some urgency because the average life expectancy is now approaching 80 years. It seems obvious for many reasons that the prime of life should be extended as far as possible toward the end of a life span. This will require attention to the processes of aging and to the role of a genetic and cultural heritage, as well as to nutrition and life-styles, and to growth in useful experience and wisdom to offset the loss of energy (which some might call an inevitable increase in the entropy of the organism) that takes place with each passing year. Also, as one ages, one collects scars from the traumas of illness, injury or emotional disturbance; when these wounds do not heal, the burden of impaired health is carried on into later years. It is this residual from earlier life experiences that, together with the special health hazards of the later years, makes up the subject matter of geriatrics and separates it from gerontology. And then there are the human or humanitarian needs of persons who are beyond their prime and the social, economic, political and

even ethical impact that these needs have and will have on friends, family and society as a whole. This constitutes yet a third area of concern, the burden of which is a personal or public responsibility which falls mostly on those yet in their prime. This is a distinct dimension of the problems of an older population, which could well become the subject matter of gereology.

It seems clear that the aim of gerontology, geriatrics and gereology should be to gain a better understanding of aging beyond the prime and, more particularly, how to extend this middle stage of life for as many years as possible to avoid, postpone or diminish the dependency upon others which so often characterizes the lives of those who are past their prime. The burgeoning of this segment of the population makes the goal a matter of no small importance and no little urgency.

—MSMW

Psychotherapeutic Drugs in Medical Practice

THE ARTICLE "Psychopharmacology in Medical Practice" by Robert Sack and James Shore in this issue raises several questions that need elaboration: Are psychotherapeutic drugs overused by primary care physicians? Are drugs used in a medical model with a definite diagnosis in mind? How can the risks of treatment be minimized? How can these drugs best be used in mental disorders associated with physical illnesses?

The majority of psychotherapeutic drugs, especially the widely used antianxiety-hypnotic and antidepressant drugs, are most often prescribed by nonpsychiatric physicians. The usual estimate is that 70 percent to 80 percent of these drugs are prescribed by physicians other than psychiatrists. Allegations that these drugs are overprescribed are generally directed toward primary care physicians.

This question is most often raised about antianxiety drugs. Approximately one adult in six receives these drugs during the course of a year. However, only 1 in 16 takes these drugs for more than a month. These figures are rather constant among different countries of Western Europe as well as for the United States.[1] Considering the vast differences in social, political, economic and cultural conditions among the various countries, it seems remarkable that the range of such use is so narrow. One might speculate that a small portion of the population may require antianxiety drugs to handle stress-induced anxiety, but that the majority of stressed persons do not need drugs. About three out of four of those who use these drugs receive "substantial benefit."

The issue ultimately becomes philosophical. If one believes that drug therapy complements problem-solving procedures, be they called psychotherapy or whatever, then limited use of antianxiety drugs makes good sense. If one believes that drugs offer an easy way out, leading to avoidance of problem-solving, then any use is bad. For many physicians, as well as patients, judicious use of antianxiety drugs may be the most expedient and cost-effective way to manage emotional disability.

On the other hand, underuse of antidepressants may be the case. Too few patients are treated with these drugs, largely due to difficulties in making the diagnosis. Depression can easily be missed or the confusing array of somatic symptoms ascribed to a variety of physical illnesses. As anxiety is an inevitable accompaniment of depression, patients may be inappropriately treated with an antianxiety drug.

Another criticism is that antidepressants are often used in too small a dose or for too short a time. Many failures of antidepressants have been linked to insufficient treatment. The hope that monitoring plasma concentrations of tricyclic antidepressants might lead to a better clinical outcome has only been partially realized. One can detect the seriously under-treated patient and remedy that situation, however.[2]

The second issue raised by Drs. Sack and Shore concerns the difficulties of psychiatric diagnosis. While it is the goal of all medical practice to let diagnosis dictate treatment, psychiatric diagnosis remains primitive. Compared with the vast array of new diagnostic tests and procedures available to other branches of medical practice, psychiatric diagnosis today is not different from that of 30 years ago. Diagnoses are still based fundamentally on *soft* clinical data. The constellation of clinical

A Medical Progress article "Psychopharmacology in Medical Practice" appears elsewhere in this issue.

symptoms and signs presented by a patient, as well as their natural history in that patient, constitute the major data for diagnosis. Constant revision of diagnoses, such as in the new *Diagnostic and Statistical Manual—Third Edition* tends to redefine diagnostic terms and, in an effort to be more precise, tends to put more cases into uncertain diagnostic categories. Considering these difficulties in diagnosis, a conscientious physician will always try to make a working diagnosis on which he can base a rational treatment, but he will be willing to make a psychiatric diagnosis on less stringent criteria than he might demand for a cardiologic diagnosis.

Still another issue raised was avoidance of unnecessary risks of treatment. Even though some psychotherapeutic drugs, such as the benzodiazepines, seem to be remarkably safe, all have the potential for producing unpleasant and sometimes dangerous side effects. In dealing with side effects, to be forewarned is to be truly forearmed. If one knows the major risks from each psychotherapeutic drug, as well as the predisposing factors that increase these risks, many can be avoided. Keeping drug treatment simple by not using exotic combinations of drugs, resisting the temptation to treat a side effect of a drug with another drug, and being willing to see how the patient who has remitted can do without drugs are some reasonable approaches toward minimizing unwanted effects of these agents.

Finally, the article emphasizes the strong interplay between somatic illness and psychiatric disorder, what some of us like to term "somatopsychic disorders," the emotional reactions to physical illness. Several illustrations are given, such as that of a patient with a new myocardial infarct who became excessively excited. Even more common is the almost universal anxiety and depression experienced by such patients. Recognition that both emotional reactions are quite appropriate to the situation, providing prognostic counseling in the most optimistic terms possible, and judiciously using sedative-hypnotic drugs and delaying use of tricyclics will not only help the patient considerably but will not expose him to unnecessary dangers.

Acute agitation and excitement can be associated with a variety of medical problems and may respond very well to low doses of high-potency antipsychotic drugs. Some of these states are associated with severe illnesses monitored in the intensive care unit, the so-called "intensive care" psychosis. One must take pains to rule out physical causes of the psychosis: abnormal electrolyte values, silent bleeding, vascular accidents —such as a pulmonary embolus or stroke, various causes of hypoxemia and drug reactions. Among the drugs to watch for are the atropine-like agents, lidocaine and theophylline. Alcohol withdrawal also comes especially to mind. If psychosis persists once these causes have been ruled out, treatment is truly needed.

The traditional sedative drugs, such as the benzodiazepines or barbiturates, make matters worse by increasing confusion. Low-potency antipsychotics, with their attendant strong antiadrenergic and anticholinergic actions, are also often contraindicated. The high-potency antipsychotics have produced the best results.

Other emotional disorders that primary care physicians must often manage are those of a patient with alcohol intoxication or withdrawal. During acute intoxication a high-potency antipsychotic drug may be preferable to avoid the respiratory depression of large doses of sedative-hypnotics, to which the patient may be cross-tolerant. During alcohol withdrawal, sedative-hypnotic drugs, especially diazepam, are clearly the most useful agents.[3]

Primary care physicians are often the first to be consulted about a patient who is becoming senile. All such patients require a medical and psychiatric evaluation to make certain that they do not have a remediable cause of their apparent dementia. If they do have Alzheimer disease the best treatment is often symptomatic, with judicious use of antipsychotic drugs for controlling behavior.[4]

The main thrust of the article by Drs. Sack and Shore is the increasing interplay between general medicine and psychiatry. Patients have both bodies and minds, and when one is affected, often so is the other. The more that psychiatrists can recognize the medical problems of *psychiatric* patients, and the more that primary care physicians can recognize the psychiatric problems of *medical* or *surgical* patients, the better it will be for all patients.

LEO E. HOLLISTER, MD
Veterans Administration Medical Center
Palo Alto, California

REFERENCES

1. Parry HJ, Balter MB, Mellinger GD, et al: National patterns of psychotherapeutic drug use. Arch Gen Psychiatry 28:769-783, 1973

2. Hollister LE: Monitoring tricyclic antidepressant plasma concentrations. JAMA 241:2530-2533, 1979
3. Thompson WL, Johnson AD, Maddrey WL, et al: Diazepam and paraldehyde for treatment of delirium tremens. Ann Intern Med 82:175-180, 1975
4. Hollister LE: Drugs for mental disorders of old age. JAMA 234:195-198, 1975

Customer Satisfaction

THERE ARE SOME disturbing parallels between what has happened to the automobile industry in America and what might be happening in medicine. For years the American automobile industry held world leadership in automotive manufacturing, design and engineering innovation, and built high-quality, popular cars. And for years American medicine has led the world in the sophistication and excellence of the health care it renders. But it is clear that our once pacesetting automobile industry has fallen behind. Its leadership is no longer unquestioned and its competitive position in the marketplace has been seriously compromised. Its customers are going elsewhere in disturbing numbers.

The reasons are many. There is little doubt that government intervention with all of its costly and often stifling rules, regulations and paperwork has played a role; it may even have diverted attention and energy from a far more basic problem—that both industry leaders and workers in automobile plants lost sight of the need for efficient automobiles of appropriate design that were constructed with skill and precision. The customers became dissatisfied with the products that were offered and bought cars built elsewhere.

There are significant parallels in what is happening in health care. Clearly, government intervention with all of its costly and often stifling rules, regulations and paperwork is playing a role —and while it is getting much blame, it may also be diverting attention from a far more basic problem. Unfortunately, there are signs that medicine's leaders, as well as the members of the medical profession in general, may be losing sight of the needs felt by their *customers*—that is, both individual patients and the public. Like the customers of automobile manufacturers, patients are seeking a product that will satisfy their needs as they see them. Too many of them are beginning to look elsewhere than to medicine, as it is customarily practiced today, to answer their needs, particularly their need to feel better. This is happening at a time when the competition for these *customers* is likely to be increasing, for reasons that need not be described here.

Perhaps there is a lesson for medicine from what has occurred in the automobile industry. The lesson may be that it is time for both the medical profession's leadership and those who provide care to give more attention to what is involved in *customer* satisfaction if they are to retain leadership or even to survive in the increasingly competitive world of health care.

—MSMW

The Platelet Connection in Arteriosclerotic Disease

COMPLEX INTERACTIONS exist between the vessel wall and the circulating blood. Vessel wall injury of whatever cause sets off a series of reactions which involve the platelets, the extrinsic and intrinsic coagulation process, and alterations in the structure and function of the smooth muscle cells of the vessel wall. As currently reviewed in the two-part specialty conference on thrombosis beginning in this issue these phenomena have been implicated in the primary atherogenic process and in the development of secondary cardiovascular events including myocardial infarction, mural thrombus formation and thromboembolic phenomena.

The platelets have attracted increasing attention as the critical element in arteriosclerotic cardiovascular disease. The platelets are activated both by vessel wall injury and by thrombin production from the coagulation reaction. The arachidonic pathway in the platelet produces increased amounts of thromboxane A_2 which further enhances the clotting mechanism and stimulates the vessel to constrict. Negative feedback mechanisms within the platelet and thromboxane A_2 inhibition from the platelet and the vessel wall maintain a delicate balance to this dynamic clotting process. The end result of the localized platelet and coagulation reaction depends in large part on the rates

A two-part Specialty Conference "Thrombosis: Its Role and Prevention in Cardiovascular Events" begins elsewhere in this issue.

of the metabolic reactions within these systems that are at the present time incompletely understood.

Considerable research interest has been directed towards the interactions that take place at the interface of the intima and the circulating blood in hopes of better understanding atherogenesis. The focal nature of the atherosclerotic process suggests that the initiating factor in this disease begins in a localized region of the vessel wall, either as a primary metabolic disorder or possibly secondary to vessel wall ischemia from compromised blood flow in the vasa vasorum. These latter vessels are quite small and might be particularly vulnerable to the vasospastic and thrombotic effects of circulating platelets, especially if there is an element of reduced flow in the vasa vasorum. This hypothesis requires further investigation.

Platelets have been incriminated as a contributing factor to the development of secondary complications from atherosclerotic disease. As Drs. Harker, Thompson and Harlan point out in the current specialty conference on thrombosis, extensive clinical trials with various antiplatelet drugs (acetylsalicyclic acid, dipyridamole and sulfinpyrazone) involving more than 10,000 coronary patients have been inconclusive in proving that these agents reduce mortality or morbidity. Where does this leave us? First, we may be barking up the wrong tree, and antiplatelet drugs may have no effect in preventing secondary complications from coronary atherosclerotic disease. Second, the drugs may be only minimally effective, and thus beneficial results may be difficult to substantiate statistically due to the influence of numerous confounding factors that plague any clinical trial. In any event, the findings to date suggest questionable usefulness of the currently available antiplatelet agents, and the routine prescription of these drugs to patients after myocardial infarctions cannot be recommended at this time.

ARTHUR J. MOSS, MD
Departments of Medicine and Preventive, Family and Rehabilitation Medicine
University of Rochester
School of Medicine and Dentistry
Rochester, New York

Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

Relapsing Fever Revisited

TO THE EDITOR: We recently reported the occurrence of 30 cases of relapsing fever in the Pacific Northwest.[1] Based on prolonged delays in diagnosis and frequent recognition of cases only through their connections with other known cases, we concluded that relapsing fever is likely an underrecognized malady in this area of the country. Following publication of this report, we were contacted by several physicians who informed us of eight additional cases of this disease. Seven patients were diagnosed by physicians who had read our article in the journal and because of it specifically pursued the diagnosis of borelliosis[1] in their patients with high fevers. We present brief case summaries to highlight again the evasive nature of this diagnosis.

Reports of Cases

CASE 1. A 21-year-old woman was admitted to a hospital in Walla Walla, Washington, on September 22, 1980, with a three-day history of spiking fevers, myalgias and a rash. She and five other persons (see below) had recently cleaned out a poorly maintained cabin which was inhabited by rodents. A blood smear was initially thought to show no abnormalities and a diagnosis of influenza was made. After reading about relapsing fever in the Northwest, the consulting physician and the hospital pathologist diligently reviewed the smear and discovered spirochetes. Tetracycline was administered and recovery was uneventful.

CASES 2 THROUGH 6. Three men and two women, aged 19 to 21, were the other members of the group. Each became ill with high fevers between September 17 and 21. One of the men was also admitted to hospital in Walla Walla, Washington, where a peripheral blood smear was also found to contain spirochetes. No smears were obtained in the other four cases. All of the patients were treated with tetracycline (although the other four had become asymptomatic) and no complications or relapses occurred.

CASE 7. A 64-year-old woman went on a camping trip on August 2, 1980, during which a *flu*-like syndrome developed, with fevers to 39.5°C and myalgias. On August 18 she was seen in a Los Angeles emergency department where microscopic hematuria was detected. She was admitted for possible sepsis. A regimen of intravenously given penicillin was begun, but following the first dose, she experienced fever, chills and hypotension. No further treatment was given and she was later discharged still feeling ill. On September 2 she again visited the emergency department because of fever, headache and altered vision in the right eye. Tenderness over the right temporal artery was found and a diagnosis of temporal arteritis was made. She was subsequently admitted to the hospital twice with this diagnosis and her condition appeared to improve with prednisone therapy on both occasions. On September 11 the patient was admitted during her fifth relapse of fever. On October 2, when the patient was an outpatient receiving prednisone, an alert resident physician, who had read our report, reviewed the peripheral blood smear and confirmed the diagnosis of relapsing fever. Treatment with tetracycline was complicated by a (second) Jarisch-Herxheimer reaction but ultimately the patient recovered.

CASE 8. We received a communication from a physician in San Mateo, California, describing an illness his son had suffered in 1965. They had stayed in a recently opened cabin in the Sierra Nevada Mountains where the boy had received "flea bites." On returning home, he became ill with high spiking temperatures and nausea. These symptoms lasted three days and resolved, but he had five relapses before a diagnosis of relapsing fever was finally made after examination of a blood smear.

Discussion

These eight cases reemphasize the difficulty in making an early diagnosis of relapsing fever. It is likely that seven of the cases would have gone un-

recognized if the physicians involved had not been recently sensitized to the diagnosis. As illustrated by the last two cases, this is a particularly difficult problem when persons return to urban environs following wilderness exposure.

We believe that these cases reinforce our contention that borelliosis is underdiagnosed, and we are grateful to the physicians who provided the clinical information for this report. Articles describing this type of problem can be of great use to practicing physicians.

STEPHAN D. FIHN, MD
ERIC B. LARSON, MD, MPH
Department of Medicine
University of Washington
Seattle

REFERENCE

1. Fihn SD, Larson EB: Relapsing fever in the Pacific Northwest: An under-diagnosed illness? West J Med 133:203-209, 1980

Coronary Bypass Operations

TO THE EDITOR: I would like to express my thanks for the most comprehensive and well-written article by Miller and Ivey on selection of patients for coronary artery bypass operations (September 1980). Every physician should read this review. The authors should receive special recognition for their clarity of writing.

NORMAN H. MELLOR, MD
Corona, California

Problems Associated With Megadose Vitamin C Therapy

TO THE EDITOR: I enjoyed reading Dr. Richard W. Vilter's article in the December 1980 issue: "Nutritional Aspects of Ascorbic Acid: Uses and Abuses." His scholarly account of the biochemistry of ascorbic acid deficiency is excellent. In the article he also pointed out that megadose therapy with ascorbic acid may not be innocuous and gave a comprehensive account of the possible side effects of this form of therapy. Unfortunately, many of our patients still subscribe to the theory "a little is good, a lot must be better."

I would like to add to Dr. Vilter's long list of problems associated with megadose vitamin C therapy. With increasing frequency in the past few years, we have encountered in our general medical clinic two new clinical syndromes associated with vitamin C therapy.

The first syndrome is that of intermittent watery diarrhea unassociated with systemic symptoms. This has often prompted unnecessary sigmoidoscopy, barium enema and examination of stool specimens for ova and parasites. In several of these patients spastic colon has been erroneously diagnosed. The physiologic explanation is that large doses of ascorbic acid act as a direct acidic irritant to intestinal mucosa, resulting in increased peristalsis and thus the phenomenon of rapid bowel transit.

The second syndrome consists of urethritis symptoms, quite reminiscent of those of nonspecific urethritis, with dysuria and even clear watery discharge. The dysuria is primarily limited to the distal urethra. Extensive and expensive studies for venereal infection give negative results. Apparently, there must be occasional urethral irritation caused by the low pH of the urine resulting from ingestion of several grams of vitamin C.

Both of the above clinical syndromes usually resolve within 24 to 48 hours after cessation of megadose vitamin C therapy. These two syndromes occur with sufficient frequency that I think it is worthwhile to keep in mind whenever we see patients with the complaints of diarrhea or urethral irritation. The cure may be as simple as stopping megadose vitamin C therapy and our patients may be spared unnecessary emotional turmoil.

TOWIE FONG, MD
Chief, Adult General Medical Clinic
Kaiser Permanente Medical Center
San Francisco

Health Care Rules and Regulations

TO THE EDITOR: The editorial "Deregulation and Governance in Health Care" in the January 1981 issue by intimating a "whiff of deregulation in the air" regarding the direction the new President may take toward the health care delivery system may foster a euphoria among physicians that is premature and probably not warranted. The actual direction taken by the administration (under the guise of deregulation and promotion of competition) may be a major problem for private fee-for-service practitioners in the next several years.

The Health Policy Advisory Group to President-elect Ronald Reagan recommended support of the procompetitive strategy of dealing with the problem of health care costs.[1] The foremost proponent of the competition strategy, Professor Alain S. Enthoven, advocates as part of the competition model placing physicians in "competing economic units"[2] (read HMO's), thus ending fee-for-service practice for most physicians. "Premi-

ums would be paid to an organization that itself accepts responsibility for providing or arranging comprehensive services."[3] This obviously excludes independent practice.

Thus, while physicians as a group probably do generally feel sympathetic to deregulation as such, the very real possibility exists that they may be regulated into neat little boxes. This is a high price for one group to pay for a purported remedy to the present system's ills and all proposed "anti-regulatory" health care legislation must be closely scrutinized with this in mind.

JAMES M. MOOREFIELD, MD
President
Sacramento-El Dorado Medical Society
Sacramento, California

REFERENCES

1. Walsh WB: Report of the Chairman of the Health Policy Advisory Group to President-elect Ronald Reagan. Millwood, Virginia, Nov 14, 1980
2. Enthoven AC: The competition strategy, status and prospects. N Engl J Med 304:109-112, 1981
3. Enthoven AC: Health Plan. Reading, MA, Addison-Wesley, 1980

* * *

To the Editor: I read with interest the editorial in the January 1981 issue of the journal on "Deregulation and Governance in Health Care." I heartily agree with what it had to say.

It has been, be it a fortunate or unfortunate experience, that I have had to deal with governmental agencies during the course of my years in practice on a great many occasions for one reason or another. Sometimes it has been because of Medi-Cal, sometimes because of PSRO and sometimes because of my working relationships with foundations for medical care and health maintenance organizations. Be that as it may, I have encountered many strange, odd, and obstructive rules and regulations.

I think, however, the editorial's point that Congress and the administration may provide an answer is wishful thinking. I believe that if any survey is to be done of the tremendous number of local, county, state, municipal and federal rules and regulations that govern health care, it will have to be done by an independent agency such as the Rockerfeller foundation or the Carnegie foundation or the Robert Wood Johnson fund or something of that type. That is, what is needed is an organization that would put together a group of experts to review all of the tremendous variety of these regulations and laws and determine which ones are unnecessary or obstructive or costly. This could well be a project for a state medical association or the AMA to initiate.

I am sure many are aware of the study done by the New York Hospital Association of all the hospitals in New York state which indicated that meeting all of the rules and regulations had added something like 25 percent to patients' hospital bills.

JOHN M. KENNEY, MD
Santa Rosa, California

Appropriateness Review: An Overview

To the Editor: Under Public Law 93-641, the National Health Planning and Resource Development Act of 1974, Health Systems Agencies and State Health Planning Development Agencies (SHPDA) are to conduct certain health service reviews. Specifically, PL 93-641 directed Health Systems Agencies (HSA's) to review, on a periodic basis, all institutional health services in the HSA's health service area and to make recommendations to the SHPDA "respecting the appropriateness in the area" of the reviewed services.

Section 1513 of PL 93-641, as amended by PL 96-79, mandates three categories of review: (1) proposed use of federal funds (PUFF), (2) new institutional health services (CON) and (3) existing institutional health services (AR). It is important to understand the relationship between Certificate of Need (CON) and Appropriateness Review (AR). Certificate of Need is intended to put a cap on the health care delivery system and Appropriateness Review is intended to shrink the system. The National Health Planning and Resource Development Act might just as well be called the National Health Planning and Resource *Limitation* Act. The major functions of HSA's will be to limit capital expenditures and choke off distribution of new technologies. One of the greatest dangers in the existing planning legislation is that we will undercapitalize the health care system similar to what happened in England.

Appropriateness Review is just another attempt at cost containment. Certificate of Need was another attempt at cost containment, and it has been shown in several studies that CON does not contain costs and may actually contribute to increasing costs.

You should be aware that in passing PL 93-641, Congress did not provide HSA's with any authority over federal health facilities. These hospitals, which some studies have shown to be the most cost-ineffective, are totally unaffected by Certificate of Need and Appropriateness Review. Re-

member this when bed number discussions arise. In making the Appropriateness Review, each HSA shall at least consider the need for the service, its accessibility and availability, cost-effectiveness, acceptability, financial viability and quality of service.

There are two major aspects of AR. The *first* is the procedures which provide the form and framework of the process. The *second,* criteria and standards, provides the substantive bases for making decisions.

In talking about standards, I might recall something Albert Einstein once said: "Mediocrity thrives on standardization." It was Emerson who said, "Every individual nature has its own beauty . . . and each mind has its own method . . . a true man never acquires after rules." I would submit that the greatest danger in planning is that it will lead to studied mediocrity. What opposes the best is not the worst, but the good enough.

Once the criteria are established and the data requirements are collected, an analysis will be conducted. One basic question which has gone unanswered is "which criterion areas take precedence in decision making; once recommendations are made, then what?" The regulations do not address the issue of sanctions, neither authorizing them or prohibiting them. Nevertheless, it should be anticipated that the state may attempt to enact legislation which attaches sanctions to SHPDA findings. Such sanctions might take the form of license revocation or third-party reimbursement policies.

A critical factor generating change in the health care field has been the rapid advances made in medical technology. These changes in technology are changing the nature of diseases being treated and society's expectations of what is possible; and they are increasing the cost of facilities, equipment and specialized personnel.

Increasing quantity of services increases costs, increasing quality of service increases costs and increasing access to services increases costs. To decrease costs, which is what AR is really all about, one would have to decrease access to service, decrease quantity of service and, inevitably, decrease quality. In short, the result would be *rationing.*

We must remember that to control health cost increases one must ration the increasing utilization. When we sit and talk about procedures, criteria, standards and all the other planning jargon, we are talking about limiting access to the health care delivery system and shrinking the system. We are talking about *rationing.*

Hospitals and doctors cannot become the rationers of services. If rationing is done there are certain basic questions:

- What services can be allowed to grow?
- What services must be restricted?
- Who will be denied services—the aged, the young?
- Will services be reduced for everyone?
- Who will decide which services are to be provided?

These are public policy issues, and if people are to be excluded from receiving services, the legislative process should determine who is excluded. But we should always keep in mind what the problem *really* is and what will be the effects of the solution.

HOWARD L. LANG, MD
San Rafael, California

Items submitted for the Correspondence section should be typed double-spaced (including references) with conventional margins. The text should not exceed 600 words.

Refer to: Minkowski WL: An American physician in rural West Africa (Medicine in Perspective). West J Med 134: 267-272, Mar 1981

An American Physician in Rural West Africa

WILLIAM L. MINKOWSKI, MD, MPH, *Los Angeles*

SHARING HEALTH CARE EXPERIENCES in varied medical settings may enlighten and even entertain. In 1976 and 1977 I worked as a primary care physician in Taabo, Ivory Coast, the construction site of a major hydroelectric project. With a surgeon and two American nurses in a 15-bed hospital, we provided comprehensive health services to a large African and small European population. The extent of those services was limited both by the finiteness of our own skills and those of our African staff and, importantly, by the distance between our isolated site and the capital city, Abidjan, 300 km to the south. The style of those services was typically American. Two years later, in November and December 1979, I volunteered to work in a Spanish Catholic mission hospital with 100 beds in the bush country of Southwest Province, Cameroon. There, too, health care had its limitations, resulting from our experiential backgrounds and an often impassable 200-km dirt road that linked us with the closest major urban center. My exposure to both hospitals, to hundreds of patients who had known health care only by a village healer or at a government center, together with visits to several national health service hospitals, provided an opportunity to compare the organization and content of African with Western medical care programs, an opportunity at once instructive and humbling. What follows are some selected, necessarily abbreviated observations based on those experiences.

Dr. Minkowski is now with the Los Angeles County Department of Health Services.

Reprint requests to: William L. Minkowski, MD, MPH, 2415 Micheltorena Street, Los Angeles, CA 90039.

By American standards Ivory Coast and Cameroon are poor countries. By African standards each is relatively prosperous, enjoying the natural resources and productivity of dense forest belts, rivers and variably fertile savannah soils. Moreover, on a continent whose governmental birth and death rates have been staggering, both countries have known remarkable political stability since achieving their independence within the last two decades. Each is intent on developing its industrial and cash crop potential, with small commitments to rural health care programs. In Taabo, Ivory Coast, our small community arose, de novo, with paved streets, river water made safely potable, indoor plumbing and an always erratic supply of electric power. In contrast, Nguti, Cameroon, the prototype of an African village of thatched roof huts with dirt floors, has no safe water, plumbing or electricity. Its physical setting is exquisite, a well-rivered valley surrounded by heavily forested hills sheltering rich mammalian, reptilian, avian and insect populations. Both communities are at the same latitude, sharing similarly high temperatures, rainfall and humidities.

With its 100 beds the mission hospital in Nguti has only one general practitioner, a young Nigerian trained in Italy, and a nurse/technician staff of 11 Spanish Sisters and Brothers of the Order of St. John of God. The physician works six full days and is on call every Sunday. He has full responsibility for all medical and surgical care. His annual vacations leave the hospital without a replacement. In his absence the nurses provide services whose scope is defined by their courage to respond to patient needs. With fore-

sight the doctor takes his holiday in August, the wettest month of the year, when potholed roads discourage all but pedestrian traffic to the hospital.

Although the belief is still widely held that medical practice in tropical Africa consists largely of treating exotic parasitic diseases, in reality it encompasses the full gamut of human illness. There are, to be sure, some significant differences in experience with disease between rural Africans and a Western population—the Africans often have a marginal nutritional status; they lack the amenities of sanitation that protect efficiently against infections borne by food, water and soil; they retain a strong faith in the healing powers of both native shamans and indigenous medications, a belief that often entails perilous delays in seeking more modern health care when that is available; and, too, they have little, if any, experience with preventive care. Although most Westerners have little knowledge of schistosomiasis, onchocerciasis, leprosy and a host of other diseases endemic to tropical regions, Africans are not less familiar with tuberculosis, asthma, measles, venereal disease or hypertension.

Because modern health care is unknown to most rural Africans, it is not unusual to find adult men and women who have never seen a thermometer, nor had a stethoscope applied to the chest, much less ever known a pelvic or rectal examination. Physicians are scarce, widely scattered among the few cities and absent in the villages of the forest and savannah. A system of health care stations run by nurses or nurse-midwives is sparsely dispersed. At these clinics itinerant government doctors make erratic visits. Ambulances are few, in unreliable repair and often too distant from a medical center to be useful. Rural African hospitals are found only in the few larger communities, not easily accessible to large numbers who must walk, make use of the bush taxi system or be carried if they live far from the few roads serviced by these vehicles. These institutions bear little resemblance to those familiar to us. Striking some balance between them and our Western counterparts are the Christian mission hospitals, where physicians have been recruited from Western countries. They work with hand-me-down equipment and unreliable lines of supply. The most notable outward contrast with Western hospitals is an apparent indifference to sanitation. Our concerns for cleanliness may be compulsive, but grossly dirty floors and walls that welcome cockroaches and lizards, torn, soiled mattresses often without linen, and the occasional multiple occupancy of beds in government hospitals are scarcely compatible even with modest standards of hygiene. Add visiting families sitting, eating and sleeping on the floor, children, remarkably well behaved but at times depositing their excrement on the bed or floor, and the total picture of septic precaution is a dismal one. On the other hand, these African hospitals are keenly sensitive to the exigencies of poverty as well as to the culturally rooted needs of families to share in the care of their own sick. Beyond the element of hygiene there are other health care differences that further widen the gulf between our systems.

Animism, the predominant rural African religion, often interferes with acceptance of using modern medical services. It fosters strong concessions to the influence of supernatural forces in the final outcome of illness. Supported by the importunings of our trained African nurses in Ivory Coast, we were occasionally able to discourage the premature departure of some patients seeking therapeutic confirmation from a village healer. Yet, even among these competent professionals there still clung vestiges of their ancestral beliefs in shaman power, which diluted the persuasiveness of their arguments. Lest one too hastily impute a pejorative primitiveness to such behavior, parallel appeals to the divine or occult are not infrequent in Western societies.

Pregnancy and childbirth are regarded and managed differently in rural West Africa. Women with few exceptions are either unfamiliar with or unaccepting of the principle of birth control. As in other undeveloped countries with high mortality rates for infants and children, fertility is an invaluable asset. In such areas children are a form of insurance against the infirmities and dislocations of old age, a state whose definition must be viewed in the perspective of life spans averaging 40 to 45 years. Frequent were the comments of Ivorian and Cameroonian women that children cannot be regarded as permanent members of the family until they have survived the first six years. Thus, pregnancy and childbirth recur without planned interruption for the full reproductive life of women. My obstetric calls to a village were most often greeted by the cries of the newborn. The mother was already on her feet disposing of the placenta and grooming her infant. Only rarely did I arrive to clamp and cut the cord, to await

or gently aid the delivery of the afterbirth and to instill silver nitrate into the eyes of the child. For such services my unsolicited reward often was the generous gift of the local delicacy, a wickedly grinning, whole, cooked lizard, its long columns of sharp teeth effectively extinguishing the flickering fire of my gastronomic daring.

Community health hazards exist for everyone in rural Africa. In some measure, at times mercilessly, biting insects left their marks on all of us. Falciparum malaria is ubiquitous. Among the expatriates daily or weekly doses of chloroquine are almost always fully protective. The Africans' immunity either completely protects or mitigates the severity of infection. Schistosomal infestations are endemic in this region. For the foreigners, however, an unwarranted fear of crocodiles, water serpents and biting insects discourages all but essential work contacts with the slow-moving waters of rivers that harbor the cercariae. Despite the existence of large numbers of venomous snakes and scorpions and the widely admitted fears of inadvertent encounters with them in gardens and along walking trails in the forest, I saw very few bites from these sources. None had serious consequences. The night soil hazard for the Africans improved as they began to use toilets provided in a worker village at the dam site in Ivory Coast. However, squatting bodies at dusk and dawn were mute evidence that not all the Africans are yet prepared to adopt this change in life-style. One environmental health problem that defies geographic limits is that of alcohol. Among the Africans the traditional drink is palm wine, derived from the sap of the palm tree. Standing as cogent evidence of its universal popularity are the graveyards of topless, lifeless palms whose juices have been carefully tapped for this beverage. As the more potent Western products flow beyond the urban centers, rural health problems related to alcohol increase. I had experience with a single death from acute intoxication and one case of delirium tremens.

Life at a rural African hospital would have a nightmarish quality for the administrator of its American counterpart. With a reputation for sanitation, solicitous, competent and inexpensive care unmatched in Cameroon, the St. John of God Hospital in Nguti daily plays host to visitors deposited by bush taxis or who arrive on foot. Admission standards require no disclosure of adequate cash or private health insurance coverage. It is far less the gravity of an illness than the need for a bed that dictates inpatient status. Less than 35 percent of the bed patients whom I cared for daily merited inpatient care. The explanation is rooted in the location of mission hospitals in small communities. Regarded as superior to government institutions they attract the sick from all areas of the country. Because hostel facilities do not exist outside the few major cities, these hospitals have little choice but to admit almost everyone who seeks their care. Outpatient service is offered to those who live nearby. The cost of a room is nominal, about 75 cents in a 10-bed ward, twice that for a private bed. To those for whom these prices are excessive, admission is not denied. There is no additional charge for the non-ill spouse and children who accompany the patient and settle down under his or her bed. The cost of major surgery is about 35 dollars. Linen is changed once a week, more often if washed by a patient's family. Few rooms contain a lavatory. None has a toilet. All water is untreated, piped directly from a forest stream 2 km away. It is never tested for coliform organisms yet has never caused an outbreak of enteric disease. Glass needles and syringes are autoclaved after each use. In government hospitals multiple injections are common between sterilizations of equipment.

The control of human traffic within rural hospitals is virtually impossible because families are expected to serve many of the physical needs of their sick members: bathing the bedridden, emptying bedpans, mopping up the soils of visiting infants, encouraging adherence to schedules of orally given medications left by nurses at the bedside and, above all, feeding patients. Also, because no government or mission hospital offers food other than the parenteral variety, the nourishment of the sick depends entirely on visitors. In our American-style Ivory Coast hospital, meals were served by the project's commissary. These Western meals were not infrequently rejected by Africans for more familiar foods prepared by the family. Every rural hospital provides for the family cooks. Stone fireplaces are quickly assembled from local materials. Women and children are the traditional wood gatherers, finding windfall logs abundant in the adjacent forest. Foodstuffs are purchased each day in the village markets. The staples of rural West African diets include the root crops, a few vegetables, rice, maize, fruits and small amounts of wild game and

fish. Bread and ground nuts (peanuts) are abundant, too, the latter adding many essential nutrients to their fare.

Apart from clinical improvement the best guarantee of patient compliance with prescriptive instructions is the unshakable reverence of Africans for the efficacy of anything coming from a medicinal container. As in many Eropean countries, here, too, the guiding principle of drug therapy is that more is better. At our American hospital in Ivory Coast I battled constantly with Italian and French expatriates who found my spartan medicinal recommendations unacceptable. My Nigerian colleague at the mission hospital in Cameroon had learned his prescriptive habits in Milan. Every patient beyond infancy is first introduced to a wide assortment of drugs in the admitting room. Singly or in combination these provide iron, vitamins, chloroquine, nonsteroidal anti-inflammatory agents, parenteral penicillin, digestive enzymes, bicarbonate, antispasmodic and anthelminthic agents, liver protectors, general antiseptics and tetracyclines. Once installed in bed the drug scene reaches its zenith with the wish to give and to receive doubly fulfilled. Every somatic complaint is rewarded with the chemical promise of swift cure from the pharmacy's therapeutic cornucopia. No committee exists to monitor the medicating predilections of the hospital's lone physician. It would be a too facile criticism, albeit justified, to charge him with indiscriminate drug dispensing habits. The practice is deeply ingrained in the European and African style of medical care. Moreover, the total responsibility for all patients in a hospital with 100 beds unavoidably denies him the luxury of that painstaking pursuit of causes that ultimately permits prescriptive precision.

In the rural hospital it is the laboratory that offers the best hope of a specific diagnosis. Microbiology and hematology are its primary strengths. Sophisticated studies of cultures, biopsy specimens and biochemical panels are rarely available. Our mission hospital in Nguti imposed formidable handicaps on its technologist, granting him only eight hours per day of electric power and a small gas-fueled refrigerator. His practical repertory comprised about ten routine tests. Whatever the presenting complaint, all patients were analyzed in the same way, on the assumption that adults, at least, share an identical disease pool. With only a nonspecific test for syphilis available in a region endemic for liver disease, almost every adult has a reactive serologic test result. The hospital policy is to treat everyone with a positive VDRL. For every man a urine specimen is sedimented, smeared and Gram-stained for gonococci and for every woman a vaginal specimen is Gram-stained as well. Positive smears for gonorrhea are found in about 45 percent of all adults, reflecting an open sexual culture that makes no use of the condom. For both syphilis and gonorrhea the same dose of aqueous penicillin is given intravenously for ten days. Neither benzathene penicillin G nor ampicillin is used for treating these venereal infections.

Africans show a strong preference for the mission hospital when a choice exists. The basis for this attitude is their perceptions of a quality of humaneness without denominational difference among the mission hospitals as opposed to one of calloused indifference prevading government centers. The many patients whom I queried about local physicians in these hospitals share both the view that doctors are preoccupied with developing private practices and the common experience of having to offer an illicit payment to outpatient staff for the privilege of consulting a doctor rather than a nurse. Yet another compelling attraction of the mission hospitals is their usually well-stocked storeroom of medications and supplies, a vital part of the support system of the parent churches in Europe and the United States. These are offered to patients either at cost or without charge. Government hospitals dispense only prescriptions, which must be filled at private, more costly pharmacies.

Preventive medicine is virtually nonexistent in these countries. Prenatal care by midwives is offered at scattered clinics. Immunizations are a variable part of their services. A single injection of tetanus toxoid for the newborn is given with greatest consistency. Children born in isolated villages are at high risk of tetanus as a consequence of the widespread custom of cauterizing the cut umbilical cord with dung-contaminated soil.

The variety of human disease, both verified and presumptive, seen in rural West Africa, covers a wide spectrum. In approximately decreasing order of frequency I observed the following: intestinal parasites, led by hookworm, ascariasis and trichocephaliasis; the venereal infections; onchocerciasis; secondary anemias; hernias, most often

inguinal, not infrequently enormous and incarcerated (see Figure 1); musculoskeletal disorders; wound infections; hypertension; clinical malaria and filariasis. The usual childhood diseases, as elsewhere, have their seasonal incidences in West Africa and there make the single largest contribution to infant mortality. I missed the season in Cameroon but in Ivory Coast experienced intimately the gravity of measles and pneumonia.

There are differences in disease endemicity between the two countries for reasons that are not clear. In both I worked at 5 degrees of latitude north of the equator in forested zones with high rainfall. Life-styles are not less primitive in one than in the other. Commonly seen in the rain forests of Ivory Coast, rarely or not at all in those of Cameroon, are onchocerciasis, guinea worm, yaws (Figure 2), goiter (Figure 3), and the sexually transmitted chancroid and lymphogranuloma venereum infections. Even less explicable are the sharply delineated zones of endemicity within a small area of one country. For example, the tsetse fly is rarely seen in the village of Nguti, Cameroon. Less than 40 km to the east, within an apparently identical environment, this horned fly is abundant and with it trypanosomiasis is a major health problem.

My vote for the dramatic highlight on the stage of tropical diseases goes to guinea worm infestation (dracunculiasis). It begins with the casual, thirst-quenching sip of puddled rainwater containing the infected crustacean, *Cyclops,* and climaxes with the painful penetration of the skin of the lower extremities by the adult worm. Its diagnosis at a distance is possible in the limping man presenting with the forepart of a protruding white worm carefully wound about a matchstick designed to tease out its full length. It is the exiting worm that incites an intense, local inflammatory tissue response (see Figure 4), partially assuaged in the cooling water of a forest pool. This immersion provides the stimulus for the adult worm to discharge its eggs. Once again the scene is set for recycling.

My experiences with death were different from those at home. Sparing no age in rural Africa,

Figure 1.—An enlarged inguinal hernia.

Figure 2.—A lesion of yaws.

death is regarded as an integral part of the continuum of life. It is an event that appears to be less threatening than for Westerners. Grief, as we know it, is brief and surely softened by the revelry of the wakes. The deceased are wrapped in sheeting by the hospital staff and, when possible, transported by the family on foot to the home village. For long distances a bush taxi may be hailed and marked as a hearse, not for hire, by decorating its front with palm fronds.

Figure 3.—A West African woman with goiter.

Figure 4.—Intense, local infection produced by a guinea worm. Forepart of the worm is protruding from the wound.

For visitors communication may pose a difficult problem. When a common language is shared, meanings may still be elusive. In Ivory Coast the national tongue is French, one in which my fluency permitted a clear exchange of information. In West Cameroon the official language is English, modified to Pidgin-English in the bush country. This dialect is more recognizable as an English variant by some familiar words than by its structure. At the St. John of God Hospital I had to lean heavily on the interpretive skills of the Sisters. Patient numbers compelled me to focus interrogation on the primary complaint. Most often our three-party system elicited information clearly, if slowly. On occasion a patient's answers were conveyed to me rather colorfully. For example, two common clinical symptoms in rural African males are diarrhea and impotence. My accompanying Sister-nurse, frocked from head to toe in the traditional garb of her Order, would receive the question about bowel habits from me. Her face beatifically innocent, she would ask the patient "You no de shit fine?" Or, from the same radiant countenance, in response to my question about sexual function, emerged her direct inquiry: "Your ting, it no wake up so fine?"

The total experience in Cameroon, brief as it was, and the longer one in rural Ivory Coast were richly rewarding personally and professionally. The exposure to pathologic conditions rarely, if ever, seen at home always provides a measure of excitement and challenge. The contacts with a population desperately in need of modern health services of all kinds and so grateful for the modest help of a caring foreigner provided the greatest of satisfactions. Not the least of my gains was the profoundly moving and humbling experience of an intimate view of the devotion to their patients of the Sisters and Brothers of the Order of St. John of God. There is, as well, that special pleasure stemming from close contact with a wholly unfamiliar culture. For those readers who would regard as adventure a shorter or longer brush with another world, the opportunities are legion in every undeveloped corner of the earth. The returns on a small investment of time and professional skill are nothing less than a bumper harvest of good will.

Refer to: Sickles EA: Xeromammography versus screen-film mammography—Pros and cons of the two techniques (Information). West J Med 134:273-274, Mar 1981

Information

Xeromammography Versus Screen-Film Mammography

Pros and Cons of the Two Techniques

EDWARD A. SICKLES, MD
San Francisco

XEROMAMMOGRAPHY and screen-film mammography are the predominant techniques being used for the radiographic detection of breast cancer.[1] Xeroradiography, a technique similar to the standard photocopying process, works on the principle that x-rays partially dissipate a uniform electrical charge applied to a selenium-alloy plate, thereby producing a latent (electrostatic) radiographic image, which is subsequently *developed* by dusting the plate with charged particles of (blue) plastic powder. The colored powder is then transferred and bonded to paper by a heat-sealing process, resulting in a blue and white image. Screen-film radiography is a more conventional technique, using regular x-ray film but coupled with a radiographic *screen,* a device that converts x-rays to visible light. The advantage of the screen is that light darkens x-ray film much more efficiently than x-rays themselves, thereby producing a properly exposed image with only a small fraction of the x-rays otherwise needed.

Several differences between xeroradiography and screen-film radiography cause important disparities in the manner in which these two techniques can be adapted to breast imaging. Screen-film techniques require both uniform-thickness breast compression and very low-energy x-ray beams (25 to 28 kVp) for diagnostically acceptable images.[2] This necessitates the use of specialized x-ray equipment designed specifically for mammographic examinations.[2] Xeroradiography techniques, on the other hand, use higher-energy x-ray beams (40 to 50 kVp), produce satisfactory mammograms without uniform-thickness breast compression and, therefore, can be used successfully with standard ceiling-mounted, general-purpose x-ray units (with few exceptions, screen-film techniques cannot). As a result, xeromammography is considerably more convenient and somewhat less expensive than screen-film techniques, especially for radiology departments or offices that do a low volume of mammography work.

There are also inherent differences in image quality between xeroradiographic and screen-film mammograms that merit discussion.[1,3] The edge-enhancement property unique to xeroradiography facilitates the imaging of tiny breast calcifications, which may be the only indication, radiographic or otherwise, that breast cancer is present. Screen-film mammograms, on the other hand, have comparatively high inherent contrast, thereby facilitating the imaging of poorly defined breast masses, which also may be the only manifestation of carcinoma. Because approximately half of mammographically detectable cancer of the breast presents with microcalcifications and the other half presents as poorly defined noncalcified masses, there is no relative advantage to either technique, nor is it possible to know a priori which technique is best for an individual patient. More important, these differences in image quality between xeromammography and screen-film mammography are quite subtle and of little clinical significance. Based on my own experience involving malignant lesions radiographed with both techniques, one technique will permit carcinoma to be diagnosed with a greater degree of confidence than the other approximately 25 percent of the time, but the circumstance in which cancer is detected by one technique but not the other occurs very infrequently.[3]

Despite the lack of a substantial difference in the quality of images between xeromammography and screen-film mammography, many radiologists express a distinct preference for one or the other technique; interestingly, these personal preferences almost always are based on extensive use of one technique and little or no familiarity with the other. There is, in fact, general agreement among experienced mammographers that either technique produces excellent results, if done by skilled personnel using proper equipment. Most unfavorable experiences with the screen-film technique reported by those favoring xeromammography result from trying to adapt to screen-film imaging

The author is Chief, Mammography Section, Department of Radiology, University of California, San Francisco, School of Medicine.

Reprint requests to: Edward A. Sickles, MD, Chief, Mammography Section, Department of Radiology, M-396, University of California, School of Medicine, San Francisco, CA 94143.

the same general-purpose x-ray equipment that works so well for xeromammography; such an unfortunate combination of equipment and technique at best produces substandard images. Very few negative experiences with xeromammography have been reported by screen-film mammographers—they rarely consider switching to the xeroradiographic technique because (1) they already have invested in the necessary specialized mammography equipment; (2) xeromammography is a technique that uses much higher doses of radiation, and (3) very few breakdowns interrupt the day-to-day operation of screen-film mammography, whereas xeromammography is noted for considerable "downtime" because of repeated malfunctions in the image-processing apparatus.

Among the various differences between xeromammography and screen-film mammography, perhaps the most important concerns radiation dose; here, screen-film technique has the clear-cut advantage, being considerably lower in dose.[4] The most pertinent of the several dose determinations is the "average dose to mammary glandular tissue," and the dose for screen-film mammography is a fourth to a tenth that for xeromammography. Although it remains unclear whether the radiation risk of mammography is great enough to be clinically meaningful, there is general agreement that because the risk of radiation-induced cancer appears to be directly proportional to radiation dose, any reduction in dose is accompanied by a parallel decrease in risk. Over the past several years there has been considerable reduction in radiation doses for all mammography techniques, so that even the xeromammography breast tissue dose is now less than 1 rad per examination at most installations. Screen-film mammography doses are so low now that the lowest of these approaches the dose of a standard x-ray examination of the chest. The dose differential between the screen-film and xeromammography techniques is most meaningful when considering the screening of asymptomatic women. In this situation we face a relatively low yield of cancer detection and the cumulative dose of multiple mammographies; the benefits derived do not exceed the presumed risk by as great a margin as they do for diagnostic mammography (the one-time examination of women with signs or symptoms that suggest the possibility of breast cancer).

Xeromammography and screen-film mammography produce images of very similar quality, with only subtle, probably insignificant differences in informational content. The major differences between the two techniques are as follows: (1) xeroradiographic processing can be done using conventional x-ray units, whereas screen-film imaging requires specialized x-ray equipment and (2) screen-film mammography imparts a considerably lower dose of radiation than does xeromammography. The overall trend among radiologists is clearly toward screen-film imaging, but xeromammography still retains a substantial following, primarily because of economic considerations.

REFERENCES

1. Gold RH: Breast, *In* Steckel RJ, Kagan AR (Eds): Diagnosis and Staging of Cancer: A Radiologic Approach. Philadelphia, W.B. Saunders Co, 1976, pp 263-287

2. Logan WW, Norlund AW: Screen-film mammography technique: Compression and other factors, *In* Logan WW, Muntz EP (Eds): Reduced Dose Mammography. New York, Masson, 1979, pp 415-428

3. Sickles EA: Mammographic interpretation: False negatives and heroic positives, *In* Logan WW, Muntz EP (Eds): Reduced Dose Mammography. New York, Masson, 1979, pp 479-485

4. Hammerstein GR, Miller DW, White DR, et al: Absorbed radiation dose in mammography. Radiology 130:485-491, Feb 1979

Refer to: Heimbach DM, Engrav LH, Marvin JA: Advances in burn care (Information). West J Med 134:274-279, Mar 1981

Information

Advances in Burn Care

DAVID M. HEIMBACH, MD
LOREN H. ENGRAV, MD
JANET A. MARVIN, RN, MN
Seattle

EACH YEAR in the United States approximately 2,000,000 people sustain burns serious enough to require seeing a physician. Of these, 50,000 people are admitted to hospital and approximately 12,000 of them die.

As late as 1960 a 30 percent total body surface area (TBSA) burn carried a mortality of 50 percent. At present, in many specialized burn centers

From the Department of Surgery, University of Washington Burn and Trauma Centers, University of Washington, Harborview Medical Center, Seattle.

Submitted July 9, 1980.

Reprint requests to: David M. Heimbach, MD, Department of Surgery, ZA-16, Harborview Medical Center, 325 Ninth Ave., Seattle, WA 98104.

ABBREVIATIONS USED IN TEXT

LBS_{50} = lethal burn size in 50 percent of patients
TBSA = total body surface area (burn)

otherwise healthy patients with burns in excess of 70 percent TBSA have a 50 percent death rate. There are now reports of patients surviving with burns in exeess of 90 percent TBSA. In our burn eenter two such patients were diseharged within the past six months and both young men are back at work.

Equally important is the reduction in morbidity from signifieant burns. None of our discharged children have missed a year of sehool, and 90 pereent of our diseharged patients have regained the same level of aetivity they had before their burn within six months. This paper will explore some of the advanees responsible for these results.

The Team Concept

A burn induees one of the most complex physiologie responses known to modern medieine. An understanding of both the physiologie and psychologie responses, as well as the realization that optimum eare ean return people to an essentially normal eondition, has led to the development of specialized burn eare facilities.

These faeilities are usually self-eontained units devoted speeifically to the eare of burned patients. While the proper physieal environment is important, the amalgamation of a multidisciplinary team, all members of whieh understand the problems unique to burned patients, is the erueial faetor.

The team is led by a surgeon with a special interest and special training. To eare for a patient with a major burn, whose condition ean deteriorate in a matter of minutes, there should be a physieian instantly aecessible to the patients 24 hours a day. Our nurses undergo a specially designed six-week training program before they are given independent nursing responsibility with any patient. Physical and oecupational therapists must be dedicated, knowledgeable and imaginative to deal with eomplex joint and splinting problems. Other members of the team include a dietitian, a psychologist or psychiatrist, a recreational therapist, social workers, an operating room team including an experienced anesthesiologist, and a group of interested eonsulting physieians. Several

TABLE 1.—*Patients Who Should Be Admitted to a Specialized Burn Care Center*

- Most patients with electrical burns
- Patients with deep burns of hands, face, feet, perineum
- Children younger than 3 years old with burns
- Adults older than 65 years old with burns
- Persons with smoke inhalation in addition to burns
- Patients with associated injuries
- Any person with burns covering more than 30 percent of the total body surface area

major burn eenters also have developed a skin bank with techniques for harvesting and storage of cadaver allograft. The skin bank technieian is also a valuable member of the burn team.

The high density of personnel required and the speeialized equipment used make burn care expensive. Although cost per day is high, eost aeeounters can show a saving in "cost per disease" as the hospital stay of these patients has been notably shortened. The return to essentially normal funetion, with the resumption of a normal, produetive work-life, saves soeiety large sums of money, but exact figures are diffieult to obtain.

The Ameriean Burn Association and the Ameriean College of Surgeons' Committee on Trauma have provided guidelines for admission to a specialized eare facility. Charaeteristies of patients requiring such eare are listed in Table 1.

Prevention

More than 90 pereent of all burns are eaused by carelessness or ignoranee and, eonsequently, are totally preventable. One major advance of national signifieanee has been the widespread availability of smoke detectors. In many states they are required in all new eonstruetion. Competition among manufaeturers has made individual units available at a very reasonable eost. Unfortunately, as with automobile seat belts, fewer than 10 pereent of the general population have taken advantage of them.

The energy crisis, perhaps more than safety education, has eonvineed many people to turn their hot water heaters down to 140°F. Water, at this temperature, requires four seeonds to create a deep burn, while water at 156°F does so in less than one seeond. Balanced against this safety feature, however, is an inereased use of space heaters and wood stoves, both of which create significant burn hazards in the home. More manufacturers are

putting short cords on appliances that heat water, and some sunlamp manufacturers are making devices with an automatic timer to prevent inadvertent prolonged exposure. In regard to clothing, the fear of cancer must be balanced against the clearly disastrous consequences of clothing that is not flame retardant and which can burn completely within a few seconds.

Other devices, such as self-extinguishing cigarettes, may become available, but without increased public awareness all of such measures will have only a minimal influence on the overall number of burn victims.

Resuscitation

Most burn victims are seen by physicians who see only a few such patients each year. The improved education and ability of these physicians to begin immediate resuscitation have greatly improved initial survival and greatly decreased the incidence of renal failure, an almost always lethal complication. Many burn formulas have been developed in the past few years. Some of these are quite complex and some are potentially hazardous. All of them are successful in the resuscitation of patients, so physicians should choose the simplest formula, one which requires a single solution and minimal electrolyte monitoring.

The most commonly used formula is the so-called Baxter or Parkland formula. It consists of Ringer's lactate solution in a quantity of 4 ml per kg of body weight per percent TBSA burn, all given in the first 24 hours. Half of the total is given in the first eight hours and a fourth in each of the next two eight-hour segments. A quick calculation reveals a 70-kg patient with a 50 percent TBSA burn will require 14 liters in 24 hours, or nearly one liter per hour for the first eight hours. The prodigious amounts of fluid required sometimes leave inexperienced physicians incredulous.

The formula is only a guideline; signs of adequate resuscitation include normal mentation, urine output of 30 to 50 ml per hour in adults, a normal central venous pressure and relatively normal vital signs. With very large burns, careful monitoring of pulmonary artery wedge pressures, cardiac outputs, and blood gases have made it possible to carry out initial resuscitation successfully in almost all burn patients. When resuscitation has begun, unless the patient is to remain at the local hospital, contact should be made with a specialized burn treatment facility and planning should proceed jointly.

Smoke Inhalation

The commonest cause of death in fires remains poisoning by carbon monoxide, which has 200 times the affinity for hemoglobin of oxygen. More recent findings also suggest that carbon monoxide combines with other heme-containing pigments such as cardiac myoglobin and enzymes such as cytochrome oxidase a3. While deaths due to carbon monoxide poisoning probably are not totally a result of anoxia, the levels of carbon monoxide in hemoglobin correlate fairly well with symptoms and with outcome. At levels above 30 percent confusion and muscle weakness occur—the patient loses both the desire and the ability to escape from the smoke. Levels above 40 percent cause unconsciousness and levels above 60 percent are usually fatal. The treatment hallmark is 100 percent oxygen. With a patient breathing room air the half-life of carbon monoxide in hemoglobin is four to five hours; with 100 percent oxygen it is 45 to 60 minutes. Realization that there is a small but significant incidence of permanent or recurrent neurologic damage has led some physicians to more liberal use of the hyperbaric oxygen chamber in treating patients with significant carbon monoxide exposure (levels greater than 25 percent). Objective data that this treatment is effective are lacking but anecdotal reports are abundant.

In addition to carbon monoxide, smoke from burning pine wood contains at least 280 identifiable chemical compounds, most of which are highly irritating. The modern marvels of petrochemistry have provided flammable plastics that have countless decomposition products. The pathophysiology and the pulmonary effects of smoke inhalation are still in the descriptive phase, but precise combustion chambers and animal models are being established to characterize specific respiratory effects. It is clear that the by-products of smoke have multiple serious effects. Immediate poisoning of the cilia of the tracheobronchial stratified epithelial lining occurs. Levels of surfactant are decreased. Mucous secretion increases and the end result of all these events is microatelectasis and sometimes macroatelectasis. Small airways are affected rapidly with features of bronchiolitis. Within hours the tracheobronchial epithelium sloughs and a severe hemorrhagic tracheobronchitis results. When inhalation is severe, alveolar epithelium is disrupted, interstitial edema is formed and eventually endothelial cells are involved, resulting in typical features of adult

respiratory distress syndrome. In addition, the pulmonary alveolar macrophages are poisoned, notably diminishing their ability by chemotaxis to move toward and destroy bacteria. This effect probably accounts for the high incidence of late bacterial pneumonia. Any or all of these findings may be present in any patient. The time of their appearance is variable and can be especially treacherous when delayed for 6 to 12 hours after exposure.

The death rate is more closely associated with the size of the burn than the severity of the smoke inhalation. Early aggressive pulmonary support with ventilator control has influenced the outcome. If ventilation and oxygenation can be supported, the lung may heal spontaneously. Administration of steroids has been shown to reduce mortality, but prophylactic antibiotics have not been shown to be of any benefit. In most burn centers the majority of patients who die with burns of less than 70 percent TBSA die from or because of associated smoke inhalation.

Nutrition

A burn provides the greatest sustained stress and highest metabolic response of any known insult. The degree of hypermetabolism is to some extent related to the size of the burn, and metabolic rates can at least double by the time the burn reaches 40 percent TBSA. The appreciation of this fact and the ability to provide increased nutrition, enterally and parenterally, have had a major impact on the survival of patients with large burns. Few patients with major burns can voluntarily eat enough to provide for their metabolic requirements. The provision of continuous enteral tube feeding has enabled many burn centers to maintain 90 percent to 95 percent of the patient's original weight. Specially trained dietitians are an integral part of our burn center staff. Careful nitrogen balance studies, weight measurement and accurate assessment of nutritional intake are done each day for every patient by the dietitian. Nutrition is continued, even during episodes of sepsis, by provision of additional insulin, alteration of nutritional formulae and adjustment of the route of administration. Most burn surgeons agree that adequate nutritional support has been directly responsible for decreased mortality: a change in lethal burn size in 50 percent of patients (LBS_{50}) from about 50 percent of TBSA to the present LBS_{50} of between 70 percent and 75 percent.

Immunity Response and Infection Control

Virtually every aspect of cellular and humoral immunity is disrupted following a severe burn. The cellular impairment extends both to macrophages and lymphocytes. Recent evidence suggests that T suppressor cells actually increase in number, perhaps due to the large amount of denatured protein and other inflammatory products from the burn, with the result that most defenses are even further compromised. Patients can develop humoral antibodies to antigens such as tetanus toxoid, but anergy to cellular antigens is very common and can be improved but not eliminated by adequate nutrition.

Infection continues to be the commonest killer of burn patients. Surprisingly, the bacteriology has changed throughout the United States. In our own unit, burn wound sepsis has decreased substantially while pneumonia and pulmonary failure remain relatively constant in patients with smoke inhalation. The advent of several effective topical antibacterial agents in the 1960's brought the LBS_{50} from 30 percent to about 50 percent. All of these agents have a very broad spectrum but none of them has uniform success against all bacteria. Before World War II Gram-positive cocci killed 30 percent of burn patients during the first week after a burn. The use of penicillin diminished this, but the patients still died during the second and third week of Gram-negative infection. Topical agents kept overall bacterial growth under control in moderate-sized burns but, in larger burns, Gram-negative organisms broke through and caused invasive burn wound sepsis. By the late 1960's and early 1970's infections with *Klebsiella* and *Pseudomonas* organisms were the commonest causes of death. At a recent national conference there was a consensus that *Pseudomonas* organisms have once again become relatively unimportant pathogens, although the reason is not entirely clear. At present *Pseudomonas aeruginosa* accounts for fewer than 8 percent of the bacteremia seen at our burn center. Gram-positive organisms, particularly coagulase-positive staphylococci have again become prevalent.

In the presence of adequate topical chemotherapy the use of prophylactic penicillin has been shown to be ineffective in preventing burn wound cellulitis. The appreciation that systemic antibiotics are not delivered to the avascular burn wound has convinced most burn surgeons to use systemic antibiotics infrequently and then only

for specific culture-positive infections or severe Gram-negative sepsis.

Early Wound Closure

During the past three years at our burn center, the average hospital stay has decreased from 32 to 15 days, although the average burn size has remained constant. The factor most responsible for this has been early aggressive wound excision and grafting. While there is nothing new about this concept, the technical ability to do so with complex and careful patient monitoring, better anesthesia, availability of blood and increased surgical skills gained through experience have made these awesome surgical procedures an everyday occurrence. Patients with deep burns can not only be spared weeks of painful daily debridement and exercises, but can look forward to essentially normal function, improved cosmetic results and less time away from home, work or school.

There are two basic surgical techniques involved. For deep dermal burns (those that require more than three weeks to heal) and small full-thickness burns, the burn wound is sequentially shaved until the bed is formed of viable dermis or healthy fat. Immediate autografts can be applied to this bed, using sheet graft on cosmetically important areas, and grafts run through a special meshing machine for all other areas. If done correctly graft-take approaches 100 percent and by the time the donor sites are healed (ten days to two weeks) the patient is well. Technical judgment regarding the depth of excision is important, and blood loss can be impressive. An excision of 20 percent of the body surface may require transfusion of a patient's entire blood volume. This technique is also useful for small burns usually treated on an outpatient basis. These small areas can be excised and grafted as a *day surgical procedure* with the same good results. The key to excisional therapy is the immediate coverage of the wound with autograft or in some cases homograft.

Since graft-take on a subcutaneous bed is uncertain, large full-thickness burns are best excised with removal of the burn and subcutaneous tissue down to the investing muscle fascia. Excision to fascia can be done with a scalpel, with electrocautery and with new tools such as the laser-assisted quartz scalpel. Blood loss is less, and graft-take is more certain, but the cosmetic results are not much better than those produced by allowing burn eschar separation, with graft placement on granulation tissue. Although it is difficult to prove, we believe that these techniques have decreased mortality from large burns, and they clearly have diminished the length of time in hospital for surviving patients with major burns.

Once the burn team has become expert in the techniques, many burn centers recommend the excision and grafting of any burn that will require more than three weeks to heal. Exceptions to this are three-dimensional areas (ear, nose), palms of the hands, soles of the feet and perineum. We generally allow faces to heal for two weeks, then excise and graft all unhealed areas. This plan allows for the greatest salvage of the contours of the face with the least amount of hypertrophic scarring.

Follow-up Care, Reconstruction, Rehabilitation

With proper treatment most patients should leave the hospital with normal function. A burn victim, however, does have a chronic disease, and because scar tissue may take one to two years to fully mature the patient should be closely followed for at least that time. The discovery that pressure can minimize scarring has led to the widespread use of elastic garments for all grafted areas and all burns that require more than three weeks to heal spontaneously. Garments are worn until the scars are mature, and although inconvenient they may greatly reduce the need for future cosmetic surgical procedures. New devices, such as clear plastic face masks, and specially fabricated conformers, have made wearing these pressure devices considerably more acceptable to most patients. In our burn center close coordination between a plastic surgeon and general surgeon has been highly successful in both initial and subsequent surgical care. The early use of flaps to cover bony defects and joints, and the late use of free flaps using microvascular techniques have made reconstruction possible in cases previously considered hopeless.

Summary

The days when a burn victim was relegated to the back of the ward, left undisturbed to scream and possibly heal himself are long gone. The modern burn ward has no odor. The visitor will find children pursuing their studies with school teachers, adults exercising with a minimum of pain and a staff generally imbued with hope rather than despair. Families of patients can be reas-

sured that when smoke inhalation, preexisting disease or age greater than 65 are not factors, a patient will almost surely survive with a burn of less than 70 percent. Such a patient today not only will survive but should have an excellent chance of regaining normal function with acceptable degrees of scarring.

No single breakthrough has been responsible for this change. Rather, the adoption of techniques learned in many disciplines, improved technology and slow but progressive understanding of the pathophysiology, coupled with a multidisciplinary team of skilled and devoted people, have made the difference. This is not to say that further progress is unnecessary. Many advances and some breakthroughs are still needed: the ability to culture skin in vitro and the availability of a collagenous framework to support the skin cells, which may someday enable us to cover patients who have no available donor sites; ways to improve immune function and other host defenses, and a better understanding of scar prevention.

Voice Changes From Antihistamines

WE LOOKED FOR a number of years at children receiving antihistamines. . . . Around the vocal folds are glands that produce fluid. The amount of fluid is about 1 liter per day, so a lot of fluid is produced in this area. When a drying agent is given to a patient, there is a tendency to change the physiological balance—to change the lubrication of these very rapidly moving structures—and to bring about some changes in the voicing process. This is something that we have to be very concerned about as we work with patients with voice problems. If a patient is receiving antihistamines or antidepressants, we can anticipate that there will be, over a long period of time, some decrease in the lubrication of the vocal fold, some thickening and reddening of the arytenoids, and a subsequent change in voice.

—FRANK B. WILSON, MD, *Edmonton, Alberta*

Exracted from *Audio-Digest Otorhinolaryngology*, Vol. 12, No. 24, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1577 E. Chevy Chase Drive, Glendale, CA 91206.

ARTICLES TO READ IN OTHER JOURNALS

EDITOR'S NOTE: *Members of the Editorial Board on occasion call attention to articles they consider to be important in other journals. These titles together with a brief assessment of the articles are published for the information of our readers.*

Ritodrine Hydrochloride: A Betamimetic Agent for Use in Preterm Labor—I. Pharmacology, Clinical History, Administration, Side Effects, and Safety; II. Evidence of Efficacy

Merkatz IR, Peter JB, Barden TP

Obstetrics & Gynecology
56:1-6; 7-12, Jul 1980

DISCIPLINES: Obstetrics, Gynecology, Family Practice

READABILITY: Very Good

Ritodrine has become the first drug approved in the United States specifically for use in preterm labor. Compared with ethanol and isoxoprine it is safe and without serious side effects. Through its use the authors noted significant reduction in neonatal death and in respiratory distress syndrome, with a measurable improvement in infant gestational age and weight gain.

—E. R. W. FOX, MD
Coeur d'Alene, ID

Percutaneous Extraction of Retained Biliary Tract Stones: 661 Patients—Garland Lecture

Burhenne HJ

AJR. American Journal of Roentgenology
134:889-898, May 1980

DISCIPLINES: Radiology, General Surgery, Gastroenterology, Primary Care

READABILITY: Excellent

A succinct and easily understandable review of retained biliary tract stones. Of value not only to radiologists and surgeons, but to all physicians whose patients require biliary tract surgical procedures.

—MARSHALL ROWEN, MD
Orange, CA

The Effect of Corticosteroids and Fetomaternal Disorders on the L:S Ratio

Morrison JC, Schneider JM, Whybrew WD, et al

Obstetrics & Gynecology
56:583-590, Nov 1980

DISCIPLINES: Obstetrics, Gynecology, Family Practice, General Practice, Internal Medicine

READABILITY: Very good

To give or not to give corticosteroids to women at risk for premature delivery—that is the question. These authors conclude that in their series there was less respiratory distress syndrome (RDS) *in the treated group as compared with the group given a placebo. Patients who had fetomaternal disorders (for example, diabetes) were benefited.*

—E. R. W. FOX, MD
Coeur d'Alene, ID

Prognostic Components of the Nonreactive Nonstress Test

Ingardia CJ, Cetrulo CL, Knuppel RA, et al

Obstetrics & Gynecology
56:305-310, Sep 1980

DISCIPLINES: Obstetrics, General Practice

READABILITY: Very good

The oxytocin challenge test (OCT) *is time-consuming and expensive, and has a high rate of false-negative and false-positive results. Using nonstress testing, through abdominal manipulation or change in maternal position, these authors observed that when the fetus reacted to its own movements with heart rate acceleration, it was invariably healthy, and the stress test was usually negative.*

—E. R. W. FOX, MD
Coeur d'Alene, ID

Somatic Illness in Psychiatric Patients

Koranyi IK

Psychosomatics
21:887, Nov 1980

DISCIPLINES: All

READABILITY: Very good

A very good article for general reading. The author reviews the findings of 12 published studies and finds "Somatic conditions were directly related to the psychiatric symptoms in 9 percent to 42 percent of the cases. Approximately half of the patients' referring physicians had not diagnosed their physical illnesses." This article obviously has a message for all physicians, regardless of speciality.

—J. M. STUBBLEBINE, MD
Greenbrae, CA

Hormones and Sexuality: Effect of Estrogen and Progestogen

Dennerstein L, Burrows GD, Wood C, et al

Obstetrics & Gynecology
56:316-322, Sep 1980

DISCIPLINES: Obstetrics, Gynecology, General Practice, General Surgery

READABILITY: Very good

In this double-blind placebo-controlled crossover study of women who had had a hysterectomy and bilateral salpingo-oophorectomy, estrogen was found to stimulate sexual desire, sexual enjoyment, vaginal lubrication and orgasm. A combination of estrogen and progestogen came in second.

—E. R. W. FOX, MD
Coeur d'Alene, ID

in memoriam

California Medical Association

ASKEW, JULIUS, San Diego. Died September 27, 1979, aged 69. Graduate of the University of Arkansas School of Medicine, Little Rock, 1936. Licensed in California in 1936. Dr. Askew was a retired member of the San Diego County Medical Society.

BECKNER, GEORGE L., Torrance. Died November 25, 1980, aged 73. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1932. Licensed in California in 1946. Dr. Beckner was a member of the Los Angeles County Medical Association.

COHEN, ELI B., Pacific Palisades. Died November 23, 1979, aged 63. Graduate of the University of Illinois College of Medicine, Chicago, 1942. Licensed in California in 1943. Dr. Cohen was a member of the Los Angeles County Medical Association.

COKE, W. HOWARD, Arcadia. Died September 4, 1980, aged 83. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1929. Licensed in California in 1929. MD degree from California College of Medicine, 1962. Dr. Coke was a member of the Los Angeles County Medical Association.

COLBERT, JOHN J., Sacramento. Died December 31, 1980 in Sacramento, aged 73. Graduate of the Creighton University School of Medicine, Omaha, 1930. Licensed in California in 1948. Dr. Colbert was a retired member of the Sacramento-El Dorado Medical Society.

DRISCOLL, JOHN A., San Francisco. Died December 21, 1980 in Santa Rosa, aged 73. Graduate of the Creighton University School of Medicine, Omaha, 1934. Licensed in California in 1934. Dr. Driscoll was a member of the San Francisco Medical Society.

EDWARDS, ROBERT W., Claremont. Died January 18, 1981, aged 56. Graduate of the University of Kansas School of Medicine, Kansas City, 1948. Licensed in California in 1951. Dr. Edwards was a member of the Los Angeles County Medical Association.

EMERSON, PHILIP E., Sacramento. Died December 30, 1980 in Sacramento of cancer, aged 63. Graduate of the University of Vermont College of Medicine, 1956. Licensed in California in 1959. Dr. Emerson was a member of the Sacramento-El Dorado Medical Society.

FLAMSON, RICHARD, La Canada. Died January 7, 1981 in Newport Beach, aged 83. Graduate of the University of Texas School of Medicine, Galveston, 1920. Licensed in California in 1921. Dr. Flamson was a member of the Los Angeles County Medical Association.

HOSFORD, GEORGE NEWTON, San Francisco. Died January 20, 1981 in San Francisco, aged 85. Graduate of the University of California Medical School, Berkeley-San Francisco, 1923. Licensed in California in 1923. Dr. Hosford was a retired member of the San Francisco Medical Society.

HUFF, GEORGE D., San Diego. Died January 12, 1981 in San Diego of cerebrovascular accident, aged 86. Graduate of the University of Texas School of Medicine, Galveston, 1924. Licensed in California in 1928. Dr. Huff was a retired member of the San Diego County Medical Society.

IVENS, MILTON HERBERT, San Diego. Died December 23, 1980 in San Diego, aged 70. Graduate of the University of Manitoba Faculty of Medicine, Winnipeg, 1935. Licensed in California in 1948. Dr. Ivens was a retired member of the San Diego County Medical Society.

JACKSON, ROBERT H., La Mesa. Died December 18, 1980 in La Mesa, aged 52. Graduate of Wayne University College of Medicine, Detroit, 1955. Licensed in California in 1958. Dr. Jackson was a member of the San Diego County Medical Society.

MCCLURE, JAMES H., Orange. Died August 23, 1980, aged 58. Graduate of the Ohio State University College of Medicine, Columbus, 1950. Licensed in California in 1962. Dr. McClure was a member of the Orange County Medical Association.

MCKEE, WAYNE P., Napa. Died December 24, 1980 in Napa of kidney disease, aged 69. Graduate of the Washington University School of Medicine, St. Louis, 1938. Licensed in California in 1939. Dr. McKee was a member of the Napa County Medical Society.

MATHEWS, SAMUEL S., Beverly Hills. Died in September 1980, aged 83. Graduate of Northwestern University Medical School, Chicago, 1935. Licensed in California in 1937. Dr. Mathews was a member of the Los Angeles County Medical Association.

MOORE, FERRALL HARMAN, Cloverdale. Died January 17, 1981 in Cloverdale, aged 76. Graduate of the University of Nebraska College of Medicine, Omaha, 1932. Licensed in California in 1933. Dr. Moore was a retired member of the Mendocino-Lake County Medical Society.

PARISI, PETER J., San Jose. Died December 29, 1980 in San Jose, aged 72. Graduate of Northwestern University Medical School, Chicago, 1934. Licensed in California in 1942. Dr. Parisi was a retired member of the Santa Clara County Medical Society.

PARKER, JAMES T., Oakland. Died January 10, 1981, aged 85. Graduate of the University of California Medical School, Berkeley-San Francisco, 1927. Licensed in California in 1927. Dr. Parker was a member of the Alameda-Contra Costa Medical Association.

PASTER, ROBERT H., Los Altos. Died January 8, 1981 of complications following open-heart surgical operation, aged 46. Graduate of Dalhousie University Faculty of Medicine, Halifax, 1966. Licensed in California in 1969. Dr. Paster was a member of the Santa Clara County Medical Society.

ROSENBERGER, MAURICE D., Los Angeles. Died October 13, 1980 in Santa Monica of heart disease, aged 71. Graduate of Georgetown University School of Medicine, Washington, DC, 1936. Licensed in California in 1943. Dr. Rosenberger was a member of the Los Angeles County Medical Association.

TWISS, ARTHUR RAYMOND, Oakland. Died January 12, 1981, aged 70. Graduate of the University of Michigan Medical School, Ann Arbor, 1935. Licensed in California in 1939. Dr. Twiss was a member of the Alameda-Contra Costa Medical Association.

VINCENT, ARTHUR J., Canoga Park. Died June 5, 1980, aged 69. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1944. Licensed in California in 1944. MD degree from California College of Medicine, 1962. Dr. Vincent was a member of the Los Angeles County Medical Association.

WALDO, HARVEY HARMON, Fallbrook. Died July 15, 1980, aged 61. Graduate of the University of Nebraska College of Medicine, Omaha, 1945. Licensed in California in 1955. Dr. Waldo was an associate member of the Napa County Medical Society.

WEILAND, ALBERT S., Newport Beach. Died April 28, 1980, aged 60. Graduate of the University of Illinois College of Medicine, Chicago, 1943. Licensed in California in 1950. Dr. Weiland was a member of the Orange County Medical Association.

Utah State Medical Association

REAM, WINSTON DALE, Salt Lake City. Died December 27, 1980 in Salt Lake City, aged 47. Graduate of Stanford University School of Medicine, Palo Alto, California, 1966. Licensed in Utah in 1973. Dr. Ream was a member of the Salt Lake County Medical Society.

Washington State Medical Association

BROWN, WILLIAM C., Longbranch. Died in 1980, aged 62. Graduate of the University of Nebraska College of Medicine, Omaha, 1943. Licensed in Washington in 1944. Dr. Brown was a member of the Medical Society of Pierce County.

GOODHOPE, C. RICHARD, Edmonds. Died November 30, 1980, aged 69. Graduate of Rush Medical College, Chicago, 1937. Licensed in Washington in 1939. Dr. Goodhope was a member of the King County Medical Society.

HENRY, ROBERT T., Colfax. Died October 30, 1980, aged 73. Graduate of the University of Oregon Medical School, Portland, 1934. Licensed in Washington in 1935. Dr. Henry was a member of the Whitman County Medical Society.

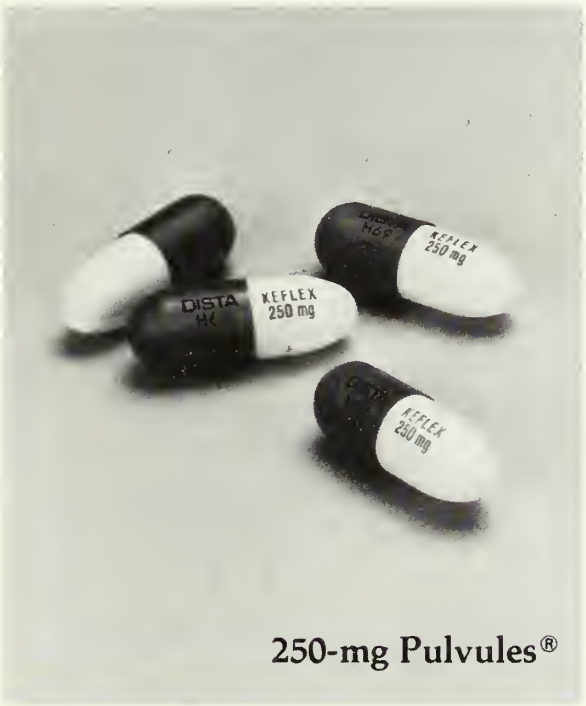
KELLY, WILLIAM J., Seattle. Died December 8, 1980, aged 60. Graduate of Temple University School of Medicine, Philadelphia, 1945. Licensed in Washington in 1946. Dr. Kelly was a member of the King County Medical Society.

LUKE, HENRY S., Seattle. Died December 11, 1980, aged 64. Graduate of Northwestern University Medical School, Chicago, 1943. Licensed in Washington in 1946. Dr. Luke was a member of the King County Medical Society.

MCCARTNEY, ROY C., Kennewick. Died December 10, 1980 in Kennewick, aged 80. Graduate of the University of Manitoba Faculty of Medicine, 1925. Licensed in Washington in 1925. Dr. McCartney was a retired member of the Benton Franklin County Medical Society.

MEAGHER, ANGUS C., Yakima. Died December 12, 1980, aged 76. Graduate of Jefferson Medical College of Thomas Jefferson University, Philadelphia, 1930. Licensed in Washington in 1932. Dr. Meagher was a member of the Yakima County Medical Society.

easy to take



250-mg Pulvules®

Oral Suspension

250 mg/5 ml
100 and 200-ml
sizes

125 mg/5 ml
60, 100, and
200-ml sizes

Pediatric Drops

100 mg/ml
10-ml size

Keflex®
cephalexin

Additional information available
to the profession on request.

DISTA

000823

Dista Products Company
Division of Eli Lilly and Company
Indianapolis, Indiana 46285
Mfd. by Eli Lilly Industries, Inc.
Carolina, Puerto Rico 00630

(Continued from Page 24)

PHYSICIANS WANTED

WESTERN ARIZONA AND SOUTHERN NEVADA —EMERGENCY MEDICINE: Clinical and Directorship positions available in several emergency departments. Excellent compensation, paid professional liability insurance, flexible scheduling. For further details contact William Salmo toll-free at 1 (800) 525-3681 (within Colorado call collect (303) 471-4981); or send credentials in complete confidence to Chase Stone Center, Holly Sugar Building, Suite 1070, Colorado Springs, CO 80903.

GENERAL SURGEON: Bd elg./cert. needed by 8-man multispecialty Group in King City, Monterey County, California, "Steinbeck Country." King City is 1 hr. from Monterey Peninsula and 3 hrs. from San Francisco. Excellent fringe benefits, opportunity to join Corp. after 6-12 months. Send CV or contact: Allan L. Fisher, MD, or Lee S. Roberts, Administrator, at Southern Monterey County Medical Group (A professional Corporation), 210 Canal St., King City, CA 93930, (408) 385-5471.

KING CITY, MONTEREY COUNTY, CALIFORNIA: "STEINBECK COUNTRY"—8-man multispecialty group is looking for 2 Family Practitioners-FP's must be willing to take OB's. Ability to speak Spanish helpful but not mandatory. King City is located 1 hr. from Monterey Peninsula and 3 hrs. from San Francisco. Excellent fringe benefits, 1st year guaranteed minimum salary, opportunity to join corporation after 6-12 months. Send CV or contact: Allan L. Fisher, MD, or Lee S. Roberts, Admin. SoMoCo Medical Group, 210 Canal St., King City, CA 93930, or telephone (408) 385-5471.

CHIEF OF PEDIATRICS—FRESNO, CALIFORNIA. The Valley Medical Center of Fresno, in affiliation with the University of California San Francisco School of Medicine is searching for a Chief of its Pediatric Service and director of the Pediatrics residency program and associated medical student clerkships. Valley Medical Center, a 400-bed county facility, is the principal teaching hospital of the UCSF Medical School's new clinical branch in the Fresno-central San Joaquin Valley region of California. The training program in pediatrics (18 residents) which places emphasis on primary care is integrated with the Valley Children's Hospital of Fresno. We seek an individual with significant background of experience in clinical teaching, research and academic administration in pediatrics who would qualify for appointment at Associate Professor or Professor level. Please direct inquiries to the chairman of the search committee: Roger Larson, MD, Assistant Dean/Director of Medical Affairs, Valley Medical Center, 445 S. Cedar Avenue, Fresno, CA 93702, (209) 453-4390.

VISTA MEDICAL GROUP, EL TORO AREA—Rapidly growing medical group needs physician for family practice and industrial medicine. (714) 837-9610.

WANTED: PEDIATRICIAN/OB/GYN/GENERAL INTERNIST—Board certified or eligible—To associate with expanding 8-man group of Multispeciality Physicians in Tacoma, Washington—Salary $40,000 per annum with partnership after first year. Send curriculum vitae or inquiries to: Clinton F. Merrill, MD, Puget Sound Clinic, 3611 South "D" Street, Tacoma, WA 98408. Or phone collect: (206) 756-8591 or (206) 589-9499 (after hours).

FAMILY PRACTITIONER—Position available in a growing and dynamic pre-paid health care plan in Spokane, Washington. This is an unusual opportunity to practice comprehensive family medicine with other well trained family practitioners without many of the distractions of office management. Continuity of care, patient education/preventative medicine, and high quality personal-style care are emphasized. Excellent salary and benefits. Ample cultural, educational, and recreational resources in our city and the surrounding countryside. Address inquiry and/or CV to James Shaw, MD, INA Healthplan of Washington, North 3919 Maple Street, Spokane, WA 99205.

FAMILY PRACTICE AND/OR EMERGENCY MEDICINE

Well established medical group seeks physicians to provide medical care service in independent practice or emergency department settings. Urban, rural or suburban areas throughout Southern CA. Substantial guarantee plus profit sharing plan and malpractice insurance. Contact:

JANIE KJORVESTAD
Pacific Physician Services
P.O. Box 1346
Loma Linda, CA 92354
(714) 825-4401

PHYSICIANS WANTED

CALIFORNIA—Primary Care Practices for Career-Oriented Primary Care physicians in Northern California. Primary care experience or residency in family practice, general practice, internal medicine or surgery. Fee-for-service compensation, guaranteed minimum, with incentives; malpractice paid. Benefits provided through affiliation with medical group. Please send curriculum vitae to: Judy Neal, California Emergency Physicians, 440 Grand Ave., Suite 500, Oakland, CA, (415) 832-6400.

PSYCHIATRIST: Associate wanted for expanding practice in Northern Los Angeles County, with access to Los Angeles without concomitant urban problems. Mixed inpatient/outpatient practice, associated with psychiatric wing of small general hospital, including unique Christian Therapy program. Seeking board certified/eligible person to work regular hours, rotate call on flexible basis for negotiable salary above $50,000 plus benefits. Contact Robert Hart, MD, 1156 East Avenue S, Palmdale, CA 93550. Tel: (805) 272-4755.

ANESTHESIA—FRESNO, CALIFORNIA. The Valley Medical Center of Fresno, in affiliation with the UCSF School of Medicine, seeks two anesthesiologists for its Department of Anesthesia. The Valley Medical Center, a 400-bed county facility, is the principal teaching hospital of the Medical School's new clinical branch in Fresno. The positions offer excellent opportunities in clinical anesthesia, teaching and research; competitive salary. Board Certification or eligibility and California license required. Please send inquiries to: Frank L. Davidson, MD, Chief of Anesthesiology, Valley Medical Center, 445 S. Cedar Avenue, Fresno, CA 93702, (209) 453-4496.

FINANCIAL REWARDS and PROFESSIONAL SATISFACTION . . . . . plus a whole lot more, Doctor!

We offer physician salaries in all specialties including General Practitioner and Family Practitioner that are among the highest paid in the nation and our benefit package (including malpractice insurance) is unexcelled.

Our quality of care is excellent; our medical facilities are attractive and efficient; and our climate for both living and working is outstanding.

We are one of the largest Federally-approved HMO's in the U.S., and we currently have a few very desirable positions available in the Los Angeles area. If you are interested, please call or write:

INA HEALTH PLAN OF CALIFORNIA
1880 Century Park East
Los Angeles, CA 90067
Phone (213) 553-6677, Extension 364
Attn.: Mr. Yoakam
Director of Physician Services

ASSOCIATES WANTED

FAMILY PHYSICIAN or other primary care: To associate with long-established board certified FP. Recent ultra-modern medical office in high income area of Orange County. Major hospital close by. Community college and Calif. State Univ. in area, teaching—UCI. Write Box 6155, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

FULL-TIME ASSOCIATE to join non-surgical orthopedic practice. Examinations, conservative care and reports required for on-the-job injured patients. Please send curriculum vitae to the Medical Director, Franklin Medical Group, 7060 Hollywood Blvd., Suite 240, Los Angeles, CA 90028, or call (213) 467-4298.

A UNIQUE FAMILY PRACTICE opening for an associate interested in OB, minor surgery, surgery assistance, general medicine, pediatrics and emergency room care. Excellent financial arrangements. Private clinic building. Our own lab and x-ray and private parking for patients. Located in northwest 25 minutes from University of Washington Medical Center. All types of recreation. Good schools. Contact J. V. Curran, MD, Claremont Clinic; 5007 Claremont Way, Everett, WA 98203. Phone (206) 259-6603.

PULMONARY ASSOCIATION now needed for rapidly growing practice in San Fernando Valley, Los Angeles. Please send CV with informative cover letter to Bern, Box 2449, Rancho Santa Fe, CA 92067.

SITUATIONS WANTED

HEMATOLOGIST-ONCOLOGIST needed for busy, aggressive practice of same in Northern California community, one and a half hours from San Francisco. Teaching available. Send CV to Box 6153, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

RADIOLOGIST, 50, CERTIFIED. Previous fellowships in cardiovascular and neuroradiology. Expertise various forms special procedures. 5 years experience neuro CT. Presently director of neuroradiology and special procedure section of large busy university affiliated hospital with faculty appointment. No preference as to location. Write Box 6157, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

INFECTIOUS DISEASE-INTERNIST. University trained, 30, ABIM certified. ID Board eligible. Desires opportunity in Infectious Disease/Internal Medicine in or near San Diego. Available July 1981. N. Kollisch, MD, 33 Pond Ave., Brookline, MA 02146. Tel (617) 566-0875.

FAMILY PRACTITIONER board qualified. Licensed California, Oregon, Washington, Minnesota. Age 47. Interested in all opportunities, prefer group practice, ER work, industrial medicine, metropolitan or rural practice. Full or part time. Contact Robert L. Stein, MD, 1215 First Ave., No. Sauk Rapids, MI 56379. Tel (612) 255-0467.

OB/GYN, 36, Univ. trained, graduated Perinatalogy Fellowship. Cal. licensed. Seeking solo, group partnership or assume practice in Southern Cal. Box 6179, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PEDIATRICIAN, 30, passed written Boards, Flex, seeks to relocate in California (Solo, Hospital based, Clinic). 1½ years in private practice. Reply Box 6175, The Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

RADIOTHERAPIST—Boards, long experience private hospital. Prefer half-time. Northern California. Will consider any California location. Reply Box 6169, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

(Continued on Page 36)

Cyriax on Orthopaedic Medicine

Mills Memorial Hospital
and
The Society of Orthopaedic Medicine
present
JAMES H. CYRIAX, M.D., M.R.C.P.

COURSE IN ORTHOPAEDIC MEDICINE

PART I: June 29 - July 2 inc.
Introduction to spinal & joint examination and treatment.

PART II: July 6-9 inc.
Advanced examination and treatment of the spine and peripheral joints.
(Attendance at previous Cyriax course required.)

held at

MILLS MEMORIAL HOSPITAL
100 SOUTH SAN MATEO DRIVE
SAN MATEO, CALIFORNIA 94401

(10 minutes from the San Francisco Airport)
Courses limited to 100 persons each
Registration deadline — May 31, 1981
CME credit 32 hours

Course in Orthopaedic Medicine
☐ Part I June 29-July 2, 1981 $345.00
☐ Part II July 6-9, 1981 $345.00
Please make check payable to
The Society of Orthopaedic Medicine
or, if using Mastercard ☐ or VISA ☐
please check appropriate box and give

_____ _____
Acct. No. Exp. date

Name _____
Last First Middle

Mailing Address _____
Number Street

_____
City State Zip

Degree _____

Daytime Phone (____) _____

Mail to 531 Cowper Street / Palo Alto, California 94301

(Continued from Page 34)

SITUATIONS WANTED

INTERNIST—certified, ICU fellowship complete, 33, interest and training in cardiology. Excellent references, available now, prefer California coast. Box 6178, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PATHOLOGIST, 45, certified AP-CP, excellent references, seeks relocation to San Francisco-San Jose area for permanent full-time or part-time practice. Box 6110, The Western Journel of Medicine, 731 Market St., Sen Francisco, CA 94103.

INTERNIST—30, ABIM certified, moving to San Diego July 1981. Seeks position in Internal Medicine. Reply Box 6167, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

RADIOLOGISTS: Plan your 1981 vacation early. Board Certified coverage for your practice. Licensed all western states. Reserve early for best selection of dates. For further information reply c/o Box 6159, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

NEPHROLOGIST—33, Board Certified, AOA, Asst. Prof. of Medicine. Desires relocation to private nephrology practice. Reply Box 6184, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

DIAGNOSTIC RADIOLOGIST desires part-time/some-time work in small community in California. Available in fall. Calvin Harstad LTC USAF, Box 1606, USAF Yokota, APO San Francisco, CA 96328.

RADIOLOGIST, diagnostic, certified ACR, with experience and training in Ultrasound, CT, Nuclear Medicine and Xerography seeking locum tenens in hospital and/or office practice. Will consider permanent association. Contact: Edward J. Barrett, MD, 4588 N. Wilson, Fresno, CA 93704. (209) 227-8163.

PATHOLOGIST, Certified in anatomic and clinical pathology, specializing in pediatric pathology and electron microscopy, 39, seeks full or part-time job. CA, AZ, NV, HI licensed. Available July, 1981. Box 6185, The Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

CARDIOLOGIST, 35, Bd. Cert. 4 yrs. post Cert. Exp. Excellent Training. Prefers full-time Hospital based cardiology position. Available July, 1981. Seeks to relocate from East Coast to California. Reply Box 6186, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

REGISTERED PHYSICAL THERAPIST seeks association with orthopedist or orthopedist group. Master's degree from USC, 3 years experience. Southern California preferred, but all California considered. Write Box 6187, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

LOCUM TENENS WANTED

LOCUM TENENS: Prestigious Sports Medicine/Preventive Medicine Center needs a board certified internist experienced in Stress Testing and giving complete physicals for one month, anytime early 1981. Write Box 6182, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

LOCUM TENENS SERVICE: Western Physicians Registry offers coverage for vacation or continuing education. To participate as temporary physician or to arrange coverage for your practice, contact: Carol Sweig, Director, 1124 Ballena Bl., Alameda, CA 94501. (415) 521-4110

PSL

PRACTICE SALES & LOCATIONS

BUY • SELL • LEASE
EVALUATIONS • FINANCE
17942 Skypark Circle, Ste D, Irvine, CA 92714
(714) 641-9203

General/Family—Internal Medicine

Industrial/Multi-Specialty Clinics
and other specialties

LOCATIONS

For Lease—Medical Bldgs—For Sale

APPRAISALS

Comprehensive practice and
property appraisals

ASSOCIATESHIPS

Placement services—Partnerships
Financing, Practice/Property Management

PRACTICES AVAILABLE

PROFESSIONAL PRACTICE OPPORTUNITIES—For help in selling/buying a medical practice, building, partnership, or finding an associate, appraisals, or physician placement. Mary Bradshaw, 21 Altamount Dr., Orinda, CA 94563. (415) 376-0762.

FOR SALE 25 year colon and rectal practice and equipment. Hollywood California area. Phone (213) 469-8289.

UNUSUAL INVESTMENT OPPORTUNITY for mature and well experienced General Practitioner. Valuable land basically smog free near ocean, Medical Office Building about 2,000 sq. ft. in excellent condition. Successful practice for many years in a prime location. No OB. Potential unlimited. Excellent Hospital facilities. Retiring physician will introduce. Terms $350,000 cash to a new loan, or submit. No equipment, furniture, or supplies. Reply P.O. Box 697, Redondo Beach, CA 90277.

BUYING or SELLING any type Medical Practice contact California Professional Practices, 2555 Huntington Dr., Suite D, San Marino, CA 91008. (213) 796-9262 or Agent Mr. Reilly (805) 543-4782 or Cliff Rauch (714) 997-0853.

LOCUM TENENS WORK WANTED

RADIOLOGIST, 50, board certified with board experience in general radiology and diagnostic ultrasound. Available for locum tenens work. Prefer Northern California. Jack Scott, MD, 11898 Forest View Dr., Nevada City, CA 95959. (916) 272-9304.

EXPERIENCED BOARD CERTIFIED OB/GYN available for locum tenens work Northern California, preferably Bay Area. Spanish second language. Available end March. (408) 258-7056.

LEGAL COUNSEL
SAMUEL SPITAL, ESQ.
1200 Third Avenue, Suite 1200
San Diego, CA 92101, (714) 231-4848
Former DEPUTY ATTORNEY GENERAL representing the Board of Medical Quality Assurance and Dept. of Health. Now specializing in B.M.Q.A. and defense malpractice matters throughout California.

MEDICAL SPACE AVAILABLE

MEDICAL SPACE AVAILABLE in Lincoln, CA, near Sacramento. Developer is seeking G.P.-Family Physician, OB/GYN, Pediatrician, Internal Medicine, Urologist to locate within new 21,000 sq. ft. Medical Ctr. to be completed February 1981. Facilities include Lab, X-ray and Pharmacy. Excellent growth area. Hewlett Packard and Shugart and Assoc. Electronics Cos. building in vicinity with 5,000 to 15,000 new employees. Will finish to suit. Contract R.S. Mgmt. Co., 541 Jefferson Ave. Suite 107, Redwood City, CA 94063. Call (415) 365-6400.

NORTHERN CALIFORNIA MOUNTAIN COMMUNITY—Medical offices, well established, retiring doctor, real estate, lg bldg, room for two practices, complete w/equip and furnishings, adaptable for dental. Owner will finance! $110,-000. Donna Woolverton, Cottage Street Real Estate, 805 Cottage St., Susanville, CA 96130. (916) 257-6994 or evenings (916) 257-2281.

SAN JOSE, Medical building 2,500 sq ft on 7,038 sq ft. lot $299,000. Near San Jose Hospital. $125,000 assumable at 13 percent. Creative financing on balance by owner. Ideal location for owner-user. Must see to appreciate. Call (408) 243-0365.

FOR LEASE—Newly remodeled medical facilities, 1,800 sq. ft. at 50 cents. Can be divided. (Pacific Manor) call day-evening, (415) 584-0331.

SANTA CRUZ—Picture yourself in the office of your dreams as you designed it. If you can we have a project you may be interested in. Medical office space for lease. Approximately 1,050 square feet available in early construction stage Leasee may be in on final design decisions. Located near Dominican Hospital in developing professional region. Expect occupancy April 1981. Please call (408) 426-4655.

MEDICAL SPACE FOR LEASE—975 or 1,700 sq. ft. Blossum Hill area-So. San Jose. MAR-LO Investments, (408) 727-1979.

BILLING/INSURANCE

on the **APPLE COMPUTER** $171 per month/lease for **COMPLETE SYSTEM** MED LOGIC SYSTEMS—2680 Walnut Ave. No. C, Tustin, CA 92680. (714) 544-8181. We discount Apple Computers. Other systems available.

TECHNICAL WRITER

TECHNICAL WRITER—Physician with medical and educational experience and technical writing training available for technical writing and editing. Clare Harper, MD, 120 Via Lerida, Greenbrae, CA 94904. (415) 461-4700.

LAB AVAILABLE

COMPLETE OFFICE LAB used under three months, includes Chem-Tek, Lyte-Tek, RIA-Phase Gamma counter, bacteriologic set-up, Cell-Trak and more. Call A. Berman, MD, (213) 596-1667.

WANTED: MEDICAL BOOKS

WANTED: MEDICAL BOOKS: Any specialty or topic for acupuncture college library. New or used. (415) 665-1200.

The Pritikin Longevity Center
A 26-day residential program for atherosclerotic disease, hypertension and diabetes mellitus

It's one thing to prescribe a nutrition and exercise plan for your patients... and it's quite another thing for most of them to do it. The Pritikin Longevity Center offers a highly successful program in lifestyle change for patients with cardiovascular disease (angina, claudication), hypertension, diabetes mellitus and other degenerative diseases. In the past five years its 26-day practical program has helped over 7,000 people learn how to live comfortably and successfully with a healthy new diet and exercise regime.

The following are some of the program's results:

- 85% of hypertensives on medication lowered their blood pressures and left the Center completely free of hypertension medication.
- 50% of adult-onset diabetics on insulin left insulin-free with controlled glucose levels.
- 61% of angina patients on medication were off their angina medication by the end of the program.
- Cholesterol and triglyceride levels were lowered on average by 25% in three weeks.*

*Statistics are based on a survey conducted by the Bio-Statistics Department of Loma Linda University of the first 893 patients at the Center.

The Center's program is supervised by physicians and is conducted in close consultation with the referring physician.

Each patient receives a physical examination and an exercise tolerance test to determine his safest, most effective exercise program. His entire exercise regime is carefully monitored by the Center's physicians and exercise physiologists.

The program also offers meals based on Nathan Pritikin's low-fat, low-cholesterol diet. Daily cooking laboratories. Nutritional counseling. A course in smoking cessation. Stress-management classes. And lectures in the degenerative diseases and their relation to diet.

Upon completion of the program the patients receive continued support through a five-year follow-up program in cooperation with the referring physician and through alumni support groups found in 30 major cities across the country.

Studies available:

1. Nutritional therapy as an alternative to coronary bypass surgery.
2. Reversal of coronary atherosclerosis: case report.
3. Summary of data on 893 patients.
4. Other studies: compliance, diabetes, claudication, mental acuity and changes in work capacity.

For more information, telephone or write:
Robert Gleser, M.D.
Medical Director
Pritikin Longevity Center
1910 Ocean Front Walk
Santa Monica, California 90405
(213) 450-5433

The predictability of an IV infusio

Until Theo-Dur there was only one method for obtaining virtually ideal therapeutic theophylli serum levels—IV infusion.

Theo-Dur provides the therapeutic benefits of I infusion in a tablet:

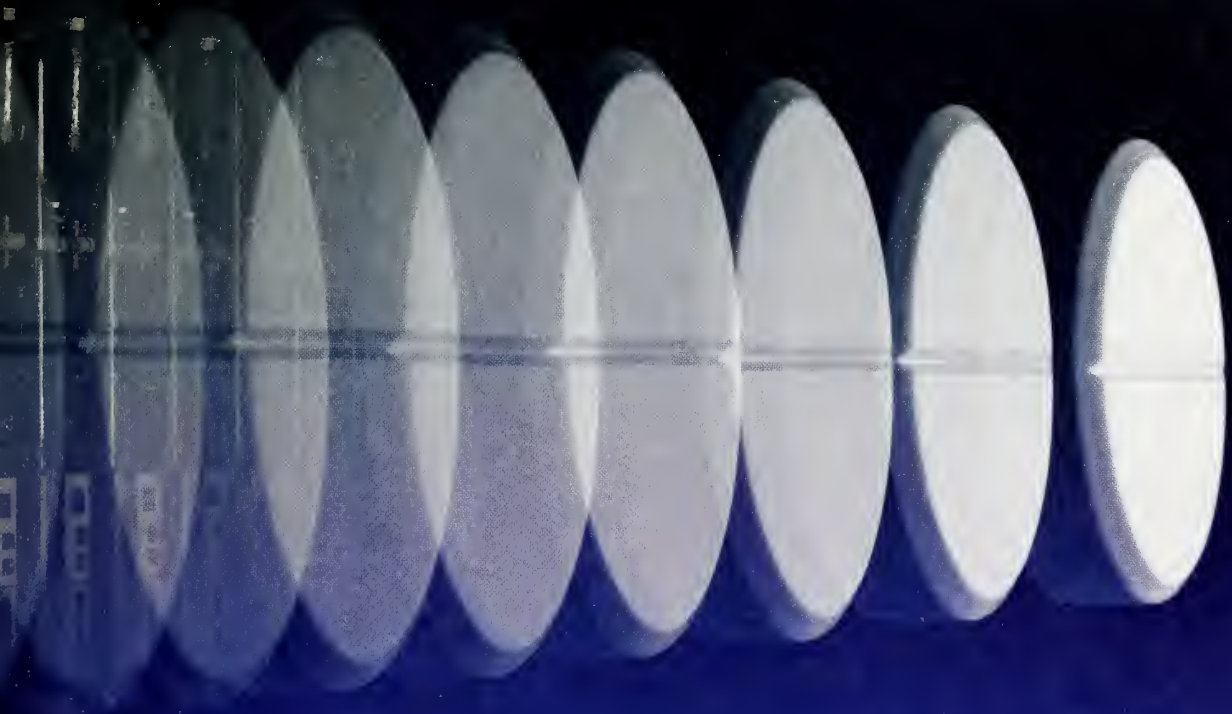
- a constant rate of theophylline absorption
- linear serum concentrations within the *therapeutic window*
- q12h dosage

© 1979 Key Pharmaceuticals, Inc.

in a tablet

Zero-Order
THEO-DUR™
(Anhydrous Theophylline)

he only formulation with q12h dosing and zero-order absorption



ZERO-ORDER dc/dt=K™
(constant rate absorption by GI infusion)

...assures programmed availability of a theophylline dose, hour by hour, for each individual, regardless of clearance rate. Thus, Theo-Dur dosage can be individualized to provide optimal results for each patient.

Theo-Dur "locks in" on the therapeutic window. Theophylline serum concentrations between 10 and 20 mcg/ml provide the *therapeutic window* within which Theo-Dur consistently provides optimal therapeutic effect for a full 12-hour interval. Blood levels above 20 mcg/ml may cause toxicity...blood levels below 10 mcg/ml may be ineffective.

Three strengths for flexible dosage. Dosage can be easily titrated for maximum therapeutic effect. Scored tablets in 100 mg, 200 mg and 300 mg strengths permit accurate dosage adjustment in as little as 50 mg increments. Patients presently on theophylline can be easily converted to Theo-Dur by dividing the daily anhydrous theophylline intake into two equal doses administered at 12-hour intervals.

Dosage and Administration: Average initial dose is 100 mg to 300 mg q12h depending on the age and weight of the patient and the severity of the disease. See package insert for full prescribing information.

See following page for a brief summary of prescribing information.

KEY PHARMACEUTICALS, INC.
Miami, Florida 33169 (USA)

THEO-DUR™

Enduring Action Anhydrous Theophylline

Sustained Action Tablets

Description: THEO-DUR Sustained Action Tablets contain anhydrous theophylline, with no color additives.

Actions: The pharmacologic actions of theophylline are as a bronchodilator, pulmonary vasodilator and smooth muscle relaxant since the drug directly relaxes the smooth muscle of the bronchial airways and pulmonary blood vessels. Theophylline also possesses other actions typical of the xanthine derivatives: coronary vasodilator, diuretic, cardiac stimulant, cerebral stimulant and skeletal muscle stimulant. The actions of theophylline may be mediated through inhibition of phosphodiesterase and a resultant increase in intracellular cyclic AMP which could mediate smooth muscle relaxation.

Indications: Symptomatic relief and/or prevention of asthma and reversible bronchospasm associated with chronic bronchitis and emphysema

Contraindications: THEO-DUR is contraindicated in individuals who have shown hypersensitivity to any of its components or xanthine derivatives.

Warnings: Excessive theophylline doses may be associated with toxicity; serum theophylline levels should be monitored to assure maximum benefit with minimum risk. Incidence of toxicity increases at serum levels greater than 20 mcg/ml. High blood levels of theophylline resulting from conventional doses are correlated with clinical manifestations of toxicity in: patients with lowered body plasma clearances, patients with liver dysfunction or chronic obstructive lung disease, and patients who are older than 55 years of age, particularly males. There are often no early signs of less serious theophylline toxicity such as nausea and restlessness, which may appear in up to 50% of patients prior to onset of convulsions. Ventricular arrhythmias or seizures may be the first signs of toxicity.

Many patients who have higher theophylline serum levels exhibit a tachycardia Theophylline products may worsen pre-existing arrhythmias.

Usage in Pregnancy: Safe use in pregnancy has not been established relative to possible adverse effects on fetal development, but neither have adverse effects on fetal development been established. This is, unfortunately, true for most anti-asthmatic medications. Therefore, use of theophylline in pregnant women should be balanced against the risk of uncontrolled asthma.

Precautions: THEO-DUR TABLETS SHOULD NOT BE CHEWED OR CRUSHED. Theophyllines should not be administered concurrently with other xanthine medications. It should be used with caution in patients with severe cardiac disease, severe hypoxemia, hypertension, hyperthyroidism, acute myocardial injury, cor pulmonale, congestive heart failure, liver disease and in the elderly, particularly males, and in neonates. Great caution should be used in giving theophylline to patients in congestive heart failure since these patients show markedly prolonged theophylline blood level curves. Use theophylline cautiously in patients with history of peptic ulcer. Theophylline may occasionally act as a local irritant to G.I. tract although gastrointestinal symptoms are more commonly central and associated with high serum concentrations above 20 mcg/ml.

Adverse Reactions: The most consistent adverse reactions are usually due to overdose and are:

Gastrointestinal: Nausea, vomiting, epigastric pain, hematemesis, diarrhea.

Central Nervous System: Headaches, irritability, restlessness, insomnia, reflex hyperexcitability, muscle twitching, clonic and tonic generalized convulsions.

Cardiovascular: Palpitation, tachycardia, extrasystoles, flushing, hypotension, circulatory failure, life threatening ventricular arrhythmias.

Respiratory: Tachypnea.

Renal: Albuminuria, increased excretion of renal tubular cells and red blood cells; potentiation of diuresis.

Others: Hyperglycemia and inappropriate ADH syndrome.

How Supplied: THEO-DUR 100 mg, 200 mg and 300 mg Sustained Action Tablets are available in bottles of 100, 1000, and 5000, and in unit dose packages of 100 (20 x 5's)

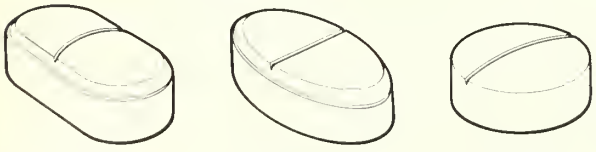
Caution: FEDERAL LAW PROHIBITS DISPENSING WITHOUT A PRESCRIPTION.

For full prescribing information, see package insert. 0779

ZERO-ORDER

dc/dt=K™

(Constant rate absorption by GI infusion)



300 mg 200 mg 100 mg

KEY PHARMACEUTICALS, INC.
Miami, Florida 33169 (USA)

The Division of

ORTHOPAEDIC SURGERY

of the

UNIVERSITY OF CALIFORNIA AT IRVINE

offers a

CRUISE

along the

MEXICAN RIVIERA

while reviewing:

Sports Medicine for the 80's

An up-to-date review of current concepts in sports medicine conducted by a group of physicians actively involved in the care of athletes. Emphasis will be placed upon the detection and treatment of sports injuries, including the prevention of problems as well as proper conditioning. This course is designed specifically for the non-orthopaedist. Forty-eight hours of learning which qualify for CME credit through the University of California, Irvine.

or

Financial Planning for the 80's

The latest approach to tackling the financial problems of the 80's, oriented to the physician's wife who is actively involved in the management of family and practice finances. A review of proper financial practices to include estate planning, investments for the 80's, corporate retirement plan management, and various other topics with ample time for discussion or questions. Thirty hours of learning.

Dates: **April 29 to May 9, 1981**

Ship: **TSS Fairsea,** Sitmar Lines

Itinerary: LOS ANGELES
CABO SAN LUCAS
MAZATLAN
ACAPULCO
ZIHUATANEJO
PUERTO VALLARTA

Cruise Prices: $1,340 to $1,758

For further information and tax data contact:
THE TRAVEL AFFAIRE
2734 East Chapman Avenue
Orange, California 92669
Phone (714) 633-5281

OFFICE EFFICIENCY

AMSI Systems Doctor Billing System for the IBM 5120: a comprehensive system in a small package.

Automated Management Services, Inc. presents a convenient automated billing, financial and statistical reporting system for the medical office. System features include:

- ☐ Insurance Receivables – automatically prepares listings of claims due to insurance companies
- ☐ Patient or Family Billing
- ☐ Printed Monthly Statements
- ☐ Financial Analysis Reports
- ☐ Printed CSC Medical Forms
- ☐ Procedure Modifier Codes
- ☐ Practice Analysis Reports
- ☐ AMA, Blue Shield, Medi-Cal Claim Forms

Our West Coast Customer Support Group is prepared to train your staff and keep the system serving the needs of your practice.

For additional information, an analysis of your needs, or to have a local representative contact you for a demonstration, call toll-free: **(800) 258-8976**

AMSI
Systems

VISIT US AT THE WESTERN SCIENTIFIC ASSEMBLY

AUTOMATED MANAGEMENT SERVICES, INC.
155 Central Street, Woodsville, N.H. 03785

(Continued from Page 21)

May 6—**Young Investigators Forum.** American Heart Assn.-Greater Los Angeles Affiliate at UCLA. Wednesday. 6 hrs. Contact: LaVerna M. Titus, AHA-GLAA, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

May 7-9—**Cardiovascular Emergencies.** American College of Cardiology and PMC at Mark Hopkins Hotel, San Francisco. Thursday-Saturday. 18 hrs. Contact: Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

May 8-10—**Cardiac Ischemia and Arrhythmias—Current Concepts for Diagnosis and Treatment.** International Medical Education Corp. at Sahara Hotel, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

May 18-21—**Endocrinology for the Practicing Physician.** LLU at Mauna Kea Beach Hotel, Kamuela, Hawaii. Monday-Thursday. 16 hrs. $200.

May 18-22—**Advances in Internal Medicine.** UCSF at Hyatt on Union Square, San Francisco. Monday-Friday.

May 23-30—**Allergy and Immunology.** Univ. of Washington School of Medicine at Wailea Beach, Maui, Hawaii. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle 98195.

May 31-June 4—**Internal Medicine for the Generalist—1981.** UCSD at Hilton, San Diego. Sunday-Thursday. 23 hrs.

June 1-5—**Advances in Internal Medicine.** UCSF. Monday-Friday.

June 3—**Gastroenterology.** St. Francis Medical Center, Lynwood. Wednesday. 6 hrs. Contact: Allan M. Hoffman, EdD, Dir. of Med. Ed., St. Francis Med. Ctr., 3630 Imperial Highway, Lynwood 90262. (213) 603-6174.

June 12-14—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Sahara Hotel, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

June 26-28—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Sheraton, Anaheim. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

July 13-17—**Third International Psoriasis Symposium.** STAN. Monday-Friday.

July 18-25—**Cardiovascular Medicine and Surgery: An Advanced Course.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 23 hrs. $295.

August 7-8—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Doubletree Inn, Monterey. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

August 21-22—**Cardiac Rehabilitation.** International Medical Education Corp. at Sheraton, Anaheim. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

September 5-11—**Dermatology.** UCD at Silverado Country Club, Napa. One week.

September 18-20—**Cardiac Ischemia and Arrhythmias—Current Concepts for Diagnosis and Treatment.** International Medical Education Corp. at Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

September 25-26—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Holiday Inn, San Francisco. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112, (800) 525-8646.

OBSTETRICS AND GYNECOLOGY

April 4-11—**Current Concepts in Ob/Gyn.** Univ. of Washington School of Medicine at Kona Surf Hotel, Kona, Hawaii. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

April 6-8—**Third Annual Orange County Ob/Gyn Congress.** Orange County Obstetrical and Gynecologic Society and UCI at Newporter Inn, Newport Beach. Monday-Wednesday. 24 hrs. $250. Contact: Orange Co. Ob/Gyn Soc., P.O. Box 1297, Orange 92668. (714) 978-1260.

April 10-11—**26th Annual T. Hart Baker, MD, Obstetrics and Gynecology Symposium.** Southern Calif. Permanente Medical Group at South Coast Plaza Hotel, Costa Mesa. Friday-Saturday. Contact: Lilia M. Guerrero, SCPMG, Dept. of Ed. and Research, 4747 Sunset Blvd., 4th Fl., Los Angeles 90027. (213) 667-4241.

April 25-30—**American College of Obstetricians and Gynecologists.** Convention Center, Las Vegas. Saturday-Thursday. Contact: W. H. McDannel, Convention Mgr., ACOG, 1 E. Wacker Dr., Suite 2700, Chicago 60601. (312) 222-1600.

May 11-13—**Recent Advances in Obstetrics and Gynecology.** UCSD at Vacation Village, San Diego. Monday-Wednesday. 18 hrs.

June 10—**Carcinomas of the Uterus and Ovaries.** See Cancer, June 10.

PEDIATRICS

April 3-4—**Pediatric Topics.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday.

April 8-10—**Update in Pediatric Pulmonary and Intensive Care.** See Medicine, April 8-10.

May 1-2—**The Physician and the Handicapped Child: New Directions.** American Academy of Pediatrics and State Dept. of Education at Sacramento. Friday-Saturday. Contact: Peter Miller, MD, Marin Co. Civic Ctr., Rm. 280, Dept. of Health and Human Services, San Rafael 94903. (415) 499-6877.

May 4-8—**11th Annual Review of Pediatrics.** USC. Monday-Friday. $300.

May 6-8—**Care of the Sick Newborn—6th Annual Symposium.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. Contact: Prog. Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

May 13—**Genetic Counseling.** LLU. Wednesday. 4 hrs. $30.

May 13—**Pediatric Symposium.** American Heart Assn.-Greater Los Angeles Affiliate and Los Angeles Pediatric Soc. at USC. Wednesday. 6 hrs. Contact: LaVerna M. Titus. AHA-GLAA, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

May 14-16—**Advances in Pediatrics.** UCSF at Mark Hopkins Hotel, San Francisco. Thursday-Saturday.

May 15-16—**23rd Annual Pediatric Symposium.** So. Calif. Permanente Medical Group at Hyatt Regency, Los Angeles. Friday-Saturday. Contact: Shirley Gach, SCPMG, Education and Research Dept., 4747 Sunset Blvd., 4th Floor, Los Angeles 90027. (213) 667-4241.

May 20-25—**Pediatrics for the Primary Care Physician and All That Jazz.** UCD at Sacramento. Wednesday-Monday.

PSYCHIATRY

April 2-4—**Short-Term Dynamic Psychotherapy.** UCSD at Hilton, San Diego. Thursday-Saturday. 17 hrs. $300.

April 2-5—**American Association of Sex Educators, Counselors and Therapists.** San Francisco. Thursday-Sunday. 24 hrs. Contact: AASECT, One E. Wacker Dr., Suite 2700, Chicago 60601. (312) 222-1717.

April 3-5—**Cults, Religiosity and the Adolescent.** UCSF. Friday-Sunday.

April 12-14—**Family Problems, Aging and Sexuality.** See Of Interest To All, April 12-14.

June 28-30—**Family Problems, Aging and Sexuality.** See Of Interest To All, June 28-30.

July 8-10—**Update in Psychiatry: Psychopharmacology.** UCSD at Hanalei Hotel, San Diego. Wednesday-Friday.

July 31-August 1—**Innovations: New Trends in Family Therapy, Brief Therapy and Family Medicine.** Mental Research Institute at Sheraton-Palace, San Francisco. Friday-Saturday. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

RADIOLOGY AND PATHOLOGY

April 8—**Apheresis Symposium.** See Medicine, April 8.

April 11-18—**Hawaii Imaging Conference.** American College of Medical Imaging at Kauai Surf Hotel, Kauai, Hawaii. One week. 23½ hrs. Contact: ACMI, P.O. Box 27188, Los Angeles 90027. (213) 275-1393.

April 25—**Cytodiagnosis in Medical Practice.** UCLA. Saturday. 6 hrs. $125.

May 2-9—**Liver Pathology Workshop.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

May 24-29—**The Pathologist as a Clinical Consultant.** UCD at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

June 1-4—**Diagnostic Cytology of the Female Genital Tract.** American Society of Clinical Pathologists at San Francisco. Monday-Thursday. 22½ hrs. $450, members; $550, nonmembers. Contact: Marian Macdonald, Admin. Asst., ASCP, 2100 W. Harrison St., Chicago 60612. (312) 738-1336.

June 3-5—**Radiology in the Emergency Room.** UCSF at Golden Gateway Holiday Inn, San Francisco. Wednesday-Friday.

June 5-7—**6th Annual Spring Diagnostic Ultrasound Conference.** L.A. Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. 17 hrs. $290. Contact: John Kassabian, MD, 100 Congress St., Pasadena 91105.

June 16-19—**Society of Nuclear Medicine.** Hilton, Las Vegas. Tuesday-Friday. 28 hrs. $60, members; $120, nonmembers. Contact: Registrar, SNM, 475 Park Ave. S., New York 10016. (212) 889-0717.

August 16-21—**23rd Annual Postgraduate Course in Dermal Pathology.** Memorial Hospital Medical Center-UCI Center for Health Education at Newporter Inn, Newport Beach. Sunday-Friday. Contact: Program Coordinator, Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

September 19—**8th Annual Radiology Symposium.** So. Calif. Permanente Medical Group at Hilton Hotel, Los Angeles. Saturday. Contact: Felecia Madison, SCPMG, Education and Research Dept., 4747 Sunset Blvd., 4th Floor, Los Angeles 90027. (213) 667-4516.

Postgraduate Videotape Programs in Diagnostic Radiology. Developed by Dept. of Radiology, UCSF. 27 programs in all aspects of diagnostic radiology. Outstanding national and international guest lecturers in addition to UC staff present basic approaches to radiographic interpretation and technique as well as new research and clinical advances. Contact: Radiology Postgraduate Ed. Section, UCSF, Dept. of Rad., Rm. M396, San Francisco 94143. (415) 666-5731, between 7:00 a.m. and 4:00 p.m.

SURGERY

March 21-22—**ECG Course for Oral and Maxillofacial Surgeons.** UCSF. Saturday-Sunday.

March 22-April 3—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. 13 days. Contact: Mrs. Mona Bolton, ERI, 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

March 25-28—**4th Annual U.S. IOL Symposium.** American Intra-Ocular Implant Society at Century Plaza Hotel, Los Angeles. Wednesday-Saturday. Contact: Debbi Miller, Dir. of Mtg. Services, Am. Intra-Ocular Implant Soc., P.O. Box 3140, Santa Monica 90403. (213) 829-7317.

March 26-28—**Retina Workshop.** St. Mary's Hospital and Medical Center at Ahwahnee Lodge, Yosemite. Thursday-Saturday. 12 hrs. $225. Contact: Retina Research Fund, St. Mary's Hosp. and Med. Ctr., 450 Stanyan St., San Francisco 94117.

March 28-29—**Common Problems in Urologic Medicine: Initial Evaluation and Management.** UCSF. Sunday-Monday.

April 4-8—**Seminar on Controversial Surgery—18th Annual.** UCLA at Hilton Riviera, Palm Springs. Saturday-Wednesday. 18 hrs. $295.

April 5-10—**Management of Maxillofacial Trauma.** Sacramento Society of Otolaryngology and Maxillo-Facial Surgery at South Lake Tahoe. Sunday-Friday. 32 hrs. $400. Contact: Sacramento Soc. of Otolaryngology and Maxillo-Facial Surgery, P.O. Box 3213, El Macero 95618.

April 8—**Urology.** St. Francis Medical Center, Lynwood. Wednesday. 6 hrs. Contact: Allan M. Hoffman, EdD, Dir. of Med. Ed., St. Francis Med. Ctr., 3630 Imperial Highway, Lynwood 90262. (213) 603-6174.

April 8-11—**Facial Plastic Surgery: Aesthetic Contouring of the Face and Neck.** UCSF at Stanford Court, San Francisco. Wednesday-Saturday. 21 hrs. $350.

April 8-12—**Symposium on Vascular Surgery—9th Annual.** UCLA at Hilton Riviera, Palm Springs. Wednesday-Sunday. 17 hrs. $315.

April 9-10—**Diseases of the Urinary Tract.** STAN at Rickey's Hyatt House, Palo Alto. Thursday-Friday. 16 hrs. $200.

April 9-11—**General Surgery.** UCSF. Thursday-Saturday.

April 23-24—**XII Jules Stein Lecture and Annual Postgraduate Seminar—Anterior Segment Disease: Current Update on Immunology, Corneal Disease, Refractive Surgery, and Contact Lenses.** Jules Stein Eye Institute, Los Angeles. Thursday-Friday. 16 hrs. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024. (213) 825-4617.

April 25—**Radial Keratotomy Workshop.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024. (213) 825-4617.

May 3-4—**6th Annual Clarence E. Stafford Memorial Surgical Symposium and Lecture—Update in Surgery of the Gallbladder and Biliary Tract.** White Memorial Medical Center and LLU at Hilton Hotel, Los Angeles. Sunday-Monday. 16 hrs. $200. Contact: Dir., Cont. Med. Ed., White Mem. Med. Ctr., 1720 Brooklyn Ave., Los Angeles 90033. (213) 268-5000, ext. 1460.

May 5-8—**2nd Annual Verne T. Inman Lectureship and 16th Annual Scientific Program of the LeRoy C. Abbott Orthopaedic Society.** UCSF. Tuesday-Friday. 14 hrs. Contact: Eileen Gaines, Alumni Sec., UCSF, U 471, San Francisco 94143. (415) 666-1166.

May 9-16—**Management of the Surgical Patient.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 25 hrs. $295.

May 21-22—**Neurosurgery—11th Annual Postgraduate Course.** UCSF. Thursday-Friday.

May 21-23—**Retina Workshop.** St. Mary's Hospital and Medical Center at Quail Lodge, Carmel Valley. Thursday-Saturday. 12 hrs. Contact: Retina Research Fund, St. Mary's Hosp. and Med. Ctr., 450 Stanyan St., San Francisco 94117.

May 22-23—**Vitrectomy-Ocutome Workshop.** PMC. Friday-Saturday. 12 hrs. $450.

June 1-5—**Intensive Course in Refractive Keratoplasty: Barraquer Technique.** Jules Stein Eye Institute, Los Angeles. Monday-Friday. $1,500. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024.

June 5-6—**Ophthalmology Update.** UCD, PMC, UCSF, STAN at Sheraton-Palace, San Francisco. Friday-Saturday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062.

June 6-12—**Orthopaedic Review Course.** UCSF at Golden Gateway Holiday Inn, San Francisco. One week.

June 20-27—**Ophthalmology.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. $350.

June 26-27—**Surgery Trauma.** UCLA. Friday-Saturday.

September 18-19—**Ophthalmology Update.** UCD, PMC, UCSF, STAN at Sheraton-Palace, San Francisco. Friday-Saturday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062.

September 19—**Oxygen Transmission and Extended Wear Contact Lenses.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024.

OF INTEREST TO ALL PHYSICIANS

March 16-20—**Sports Medicine.** University of Hawaii at Princess Kaiulani Hotel, Waikiki, Honolulu. Monday-Friday. 18 hrs. $230. Contact: Joy Lewis, Box CE-CCECS, 2530 Dole St., Honolulu 96822. (808) 948-8244.

March 16-27—**Intensive Residency in Occupational Medicine, Session II.** UCSF. Two weeks.

March 18-20—**Recent Advances in Clinical Nutrition.** UCSD at Vacation Village, San Diego. Wednesday-Friday. 17 hrs.

March 21—**Alcoholism and Its Treatment: 1981.** UCD at Hotel El Rancho Racquet Resort, Sacramento. Saturday. 7½ hrs.

March 21-22—**Sleep and Biological Rhythms.** UCSD. Saturday-Sunday.

March 25-29—**Human Dimensions in Medicine.** UCSD at Vacation Village, San Diego. Wednesday-Sunday. 26 hrs. $400.

April 1-2—**Symposium on Infectious Diseases.** Sutter Community Hospitals at Northeast Holiday Inn, Sacramento. Wednesday-Thursday. 14 hrs. $85. Contact: Sutter General Hospital, Cont. Med. Ed., 2820 L St., Sacramento 95816. (916) 454-2222, ext. 1430.

April 8—**Psychiatry for the Non-Psychiatrist.** LLU. Wednesday. 4 hrs. $30.

April 8—**Rehabilitation of the Elderly Patient.** La Palma Intercommunity Hospital and UCI at South Coast Plaza Hotel, Costa Mesa. Wednesday. $75. Contact: Ingrid Humphrey, La Palma Intercommunity Hosp., 7901 Walker St., La Palma 90623. (714) 522-0150.

April 11-12—**Nutrition for the Primary Care Physician.** UCSF. Saturday-Sunday. 14 hrs. $125.

April 11-18—**Office Management of Chronic Pain.** Univ. of Washington School of Medicine at Wailea Beach, Maui. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

April 11-18—**Drug Therapy.** Univ. of Washington School of Medicine at Royal Lahaina, Maui. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

April 12-14—**Family Problems, Aging and Sexuality.** USC. Sunday-Tuesday. 18 hrs. $136.

April 23-25—**Postgraduate Institute.** CMA at Ahwahnee Hotel, Yosemite. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

April 23-26—**Wound Management Workshop.** UCSD at Hilton, San Diego. Thursday-Sunday. 20 hrs.

April 24-25—**Fluid and Electrolytes.** PMC. Friday-Saturday. 12 hrs.

April 25-26—**Pharmacokinetics '81.** Memorial Hospital Medical Center—UCI Center for Health Education, Long Beach. Saturday-Sunday. Contact: Prog. Coordinator, Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

April 25-May 2—**Diagnostic and Therapeutic Skills.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $350.

May 1-2—**Annual Spring Seminar.** Providence Hospital at Claremont Hotel, Oakland. Friday-Saturday. Contact: Providence Hosp., Med. Staff Office, Box 23020, Oakland 94623. (415) 874-8003.

May 5-11—**Basic Diving Medicine.** UCSF at Fresno and Monterey. One week.

May 7-8—**Advances in Infectious Diseases—Sexually Transmitted Diseases in Clinical Practice.** UCSF. Thursday-Friday.

May 11-15—**Postgraduate Institute for Primary Care Physicians—Symposium on Non-Emergency Outpatient Care.** UCSD at Vacation Village, San Diego. Monday-Friday. 27 hrs. $275.

May 16—**Otolaryngology for the Primary Care Physician.** Institute for Medical Education and Research and UCSD at Cafe del rey Moro, San Diego. Saturday. 8 hrs. $70. Contact: Karen Delaney, Inst. for Medical Education and Research, 135 Dickinson St., San Diego 92103. (714) 272-3126.

May 16-17—**Eating Disorders.** UCLA. Saturday-Sunday.

May 17-22—**Fingers-to-the-Toes: An Orthopedic Approach for the Family Physician.** UCD at Stanford Sierra Lodge, Fallen Leaf Lake. Sunday-Thursday.

May 31-June 6—**Family Practice Refresher Course.** UCLA at Miramar-Sheraton, Santa Monica. One week.

June 7-13—**Family Practice Refresher Course.** UCI at Disneyland Hotel, Anaheim. One week. 53 hrs. Contact: Cont. Ed. in Health Sciences, UCI Extension, P.O. Box AZ, Irvine 92716. (714) 833-5414.

June 8-12—**Family Practice Board Review Course.** UCSF. Monday-Friday.

June 10-12—**6th Annual Conference on Hyperbaric Oxygen.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. Contact: Program Coordinator, Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

June 11-13—**Human Sexuality.** CMA at Claremont Resort, Oakland. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

June 12-14—**Clinical Update.** American Medical Association at Hilton, San Francisco. Friday-Sunday. Contact: AMA Dept. of Meeting Services, 535 N. Dearborn St., Chicago 60610. (312) 751-6000.

June 28-30—**Family Problems, Aging and Sexuality.** USC. Sunday-Tuesday. 17¼ hrs. $136.

August 16-21—**9th Annual Family Practice Refresher Course.** UCD at Hyatt Del Monte, Monterey. Sunday-Friday. 36 hrs.

September 7-18—**Intensive Residency in Occupational Medicine, Session III.** UCSF. Two weeks.

Needs Identification and Fulfillment Tailored to the Individual (NIFTI). UCSF. A new contemporary approach to formal continuing medical education. Participating physicians identify their own CME needs which will be met by a program specifically tailored by UCSF faculty for each individual physician. 25 hrs. minimum; 100, maximum. Fee: $350; $200, UCSF alumni. Contact: Extended Programs in Medical Education, 569-U, Univ. of Calif., San Francisco 94143. (415) 666-4251.

Audio-Digest Foundation—A nonprofit subsidiary of CMA. Provides by subscription twice-a-month tape recorded summaries of leading national meetings and authoritative surveys of current literature. A catalog of lectures and panel discussions in all areas of medical practice is also available. Contact: Audio-Digest Foundation, 1577 E. Chevy Chase Dr., Glendale 91206.

Videotape Postgraduate Course for the Primary Care Physician. UCSF, School of Medicine, Div. of Ambulatory and Community Medicine. 24 Category I hrs. upon completion of course as designed—12 programs each year. Contact: Ms. Estelle Nelson, UCSF, Rm. 432-A, 400 Parnassus Ave., San Francisco 94143. (415) 666-1445.

ALASKA, MONTANA and IDAHO

This list of continuing education programs in Alaska, Montana and Idaho is supplied by the University of Washington School of Medicine's program of regional medical education in Washington, Alaska, Montana and Idaho (WAMI). To have events listed, please send information to: WAMI Program, CME Calendar, D-207 Health Sciences Building, School of Medicine, SC-64, University of Washington, Seattle, Washington 98195; or phone (206) 543-6995.

ALASKA

March 19—**Right Brain Functioning—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday, 7:30 pm-9:30 pm. Alaska Psychiatric Institute Medical Library. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99503. (907) 274-7579.

March 25—**Gardnerella Vaginalis Vaginitis—Univ. of Wash. Ob/Gyn Sessions** (Anchorage). Wednesday, 12-1 p.m. Providence Hospital. Contact: Hedric Hanson, MD, 3300 Providence Drive, Anchorage, AK 99504. (907) 276-8385.

April 30—**Group Therapy—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday, 7:30 pm-9:30 pm. Alaska Psychiatric Institute Medical Library. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99503. (907) 274-7579.

May 27—**Univ. of Wash. Ob/Gyn Session** (Anchorage). Wednesday, 12-1 p.m. Providence Hospital. Contact: Hedric Hanson, MD, 3300 Providence Drive, Anchorage, AK 99504. (907) 276-8385.

June 18—**Consultation on Adolescent Problems/Systems Approach—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday, 7:30 pm-9:30 pm. Alaska Psychiatric Institute Medical Library. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99503. (907) 274-7579.

MONTANA

March 25-27—**New Developments in Cardiology—Univ. of Wash. Internal Medicine Review Sessions.**

March 25, Wednesday, Great Falls. 5-7:30 p.m., Columbus Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

March 26, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: D. Frank Johnson, MD, Marillac Hall, Billings, MT 59101. (406) 657-7083.

March 27, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

April 15—**Pediatric Psychiatry—Univ. of Wash. Pediatrics Sessions** (Great Falls). Wednesday. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

April 22-24—**Congenital Heart Disease in Adults—Univ. of Wash. Internal Medicine Review Sessions.**

April 22, Wednesday, Great Falls. 5-7:30 p.m., Deaconess Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

April 23, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: D. Frank Johnson, MD, Marillac Hall, Billings, MT 59101. (406) 657-7083.

April 24, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

May 27-29—**Office Endocrinology—Univ. of Wash. Internal Medicine Review Sessions.**

May 27, Wednesday, Great Falls. 5-7:30 p.m. Columbus Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

May 28, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: D. Frank Johnson, MD, Marillac Hall, Billings, MT 59101. (406) 657-7083.

May 29, Friday, Missoula. 8-10:30 a.m. St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

June 10—**Allergy—Univ. of Wash. Pediatrics Sessions** (Great Falls). Wednesday. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

IDAHO

March 16—**Gyn Oncology—Univ. of Wash. Ob/Gyn Sessions** (Boise). Monday. 12-1 p.m., St. Luke's Hospital. Contact: David M. Barton, MD, 999 N. Curtis Rd., Boise, ID 83706. (208) 385-9391.

(Continued on Page 49)

for your patients with moderate depression and anxiety

RELIEF WITHOUT A

The choice without a phenothiazine

☐ provides the specifically effective antianxiety action of Librium® (chlordiazepoxide HCl/Roche), with its outstanding safety record, together with the well established antidepressant effect of amitriptyline.

☐ symptoms likely to respond in the first week of treatment include insomnia, anorexia, psychic and somatic anxiety, agitation and feelings of guilt or worthlessness.

A better choice because

☐ minimizes risk of tardive dyskinesia and other extrapyramidal side effects. The caus relationship between the phen thiazines and extrapyramidal side effects, including tardive dyskinesia, is well established In contrast, the reported incidence of these adverse reactions with Limbitrol or eith of its components is rare.

ROCHE®

HENOTHIAZINE

What
better reason
to switch from
a phenothiazine
combination
and start prescribing

Limbitrol® IV

Tablets 5-12.5 each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)
Tablets 10-25 each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt)

Please see following page for summary of product information.

LIMBITROL® TABLETS Tranquilizer—Antidepressant

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Relief of moderate to severe depression associated with moderate to severe anxiety

Contraindications: Known hypersensitivity to benzodiazepines or tricyclic antidepressants. Do not use with monoamine oxidase (MAO) inhibitors or within 14 days following discontinuation of MAO inhibitors since hyperpyretic crises, severe convulsions and deaths have occurred with concomitant use, then initiate cautiously, gradually increasing dosage until optimal response is achieved. Contraindicated during acute recovery phase following myocardial infarction.

Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

Usage in Pregnancy: **Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage; withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline; symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).

Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication; and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. Concomitant use with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy.

Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.

Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.

The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs:

Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.

Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido.

Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.

Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.

Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.

Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.

Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female and elevation and lowering at blood sugar levels.

Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single h.s. dose may suffice for some patients. Lower dosages are recommended for the elderly.

Limbitrol 10-25, initial dosage of three to four tablets daily in divided doses, increased up to six tablets or decreased to two tablets daily as required. Limbitrol 5-12.5, initial dosage of three to four tablets daily in divided doses, for patients who do not tolerate higher doses.

How Supplied: White, film-coated tablets, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt) and blue, film-coated tablets, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt) — bottles of 100 and 500; Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25; and in boxes containing 10 strips of 10; Prescription Paks of 50.

ROCHE®

ROCHE PRODUCTS INC.
Manati, Puerto Rico 00701

Your guide to patient management... when you decide medication is needed

How to initiate and maintain therapy

Select dosage strength appropriate for each patient

- Limbitrol 5-12.5 is recommended to minimize drowsiness and for elderly patients
- Limbitrol 10-25 may be indicated for patients who tolerate medication without undue side effects

Specify daily dosage based on symptom severity

- An initial dosage of three tablets is recommended
- Dosage may be increased to six tablets or decreased to two tablets daily as necessary
- Once a satisfactory response is obtained, patients should be continued on the smallest dose required to maintain the desired effect

Utilize dosage options to best accommodate individual patient needs

- T.I.D. or Q.I.D., familiar regimens most suited for patients who tolerate medication without undue drowsiness
- Two tablets one hour before bedtime and one tablet midday may minimize daytime drowsiness and help relieve a common target symptom — insomnia
- Entire dosage h.s. to take maximum advantage of the sedative effect

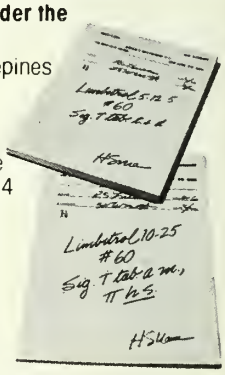
How to make each patient an informed patient

1. Discuss with patients the probability that they will experience drowsiness, especially during the first week.
2. Reassure your patients that drowsiness is one indication that the medication is working and that it may help alleviate their insomnia.
3. Encourage patients to report if drowsiness becomes troublesome so that, if necessary, dosage schedule can be adjusted.
4. Caution patients about the combined effects with alcohol or other CNS depressants. Let them know that the additive effects may produce a harmful level of sedation and CNS depression.
5. Caution patients about activities requiring complete mental alertness, such as operating machinery or driving a car.
6. Warn pregnant patients and patients of childbearing age that the safety of Limbitrol in pregnancy has not yet been established.

Please see complete product disclosure for other pertinent information.

Limbitrol should not be used under the following circumstances:

1. Hypersensitivity to benzodiazepines or tricyclic antidepressants.
2. Concomitantly with an MAO inhibitor. To replace an MAO inhibitor with Limbitrol, discontinue MAO inhibitor for a minimum of 14 days before cautiously initiating Limbitrol therapy.
3. During the acute recovery phase following myocardial infarction.



In moderate depression and anxiety

Limbitrol®

Relief without a phenothiazine

(Continued from Page 45)

March 17—**Infectious Diseases—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12-1 p.m., St. Anthony Hospital. Contact: David Fischel, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

May 18—**Evaluation and Treatment of Premature Labor—Univ. of Wash. Ob/Gyn Sessions** (Boise). Monday. 12-1 p.m., St. Luke's Hospital. Contact: David M. Barton, MD, 999 N. Curtis Rd., Boise, ID 83706. (208) 385-9391.

May 19—**Psychiatry—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12-1 p.m., St. Anthony Hospital. Contact: David Fischel, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

NEW MEXICO

All courses listed below have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the Amercan Medical Association. The Continuing Medical Education Committee of the New Mexico Medical Association has certified all courses listed below as meeting the criteria for Category 4 under the New Mexico Board of Medical Examiners Continuing Medical Education regulations.

Information and requests for accreditation should be sent to the chairman of the CME Committee, New Mexico Medical Society, 2650 Yale SE No. 105, Albuquerque, NM 87106 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 247-0539.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

March 8-11—**New Mexico Metabolism Symposium.** Taos. Sunday-Wednesday. Tennis Ranch of Taos. 12 credit hours. Contact: Office of Medical Education, Lovelace Medical Center, 5400 Gibson Blvd. SE, Albuquerque, NM 87108. (505) 842-7000.

March 9-28—**New Mexico Medical Society Sino-American Clinical Study Tour.** 50 credit hours. Contact: Professional Seminar Consultants, Inc., 3194 Lawson Blvd., Oceanside, NY 11572. (516) 536-7292.

March 10-15—**New Mexico Academy of Family Physicians Medical-Dental Ski Symposium.** Durango, Colorado. Tuesday-Sunday. Iron Horse Resort & Conference Center. 20 credit hours. Contact: David R. Holten, MD, NMAFP, 2650 Yale SE, Albuquerque, NM 87106. (505) 247-0539.

March 20—**7th Annual Alcoholism Symposium—Alcoholism in Adolescence.** Albuquerque. Saturday. Vista Sandia Hospital. Hour for hour credit. Contact: John McCormack, MD, Vista Sandia Hospital, 501 Richfield NE, Albuquerque, NM 87113. (505) 898-1661.

April 2-4—**Emergency Medicine Symposium.** Taos. Thursday-Saturday. Tennis Ranch of Taos. 18 credit hours. Contact: Arleen Sadowsky, MD, New Mexico Chapter, American College of Emergency Physicians, 6320 Palma Pl. NW, Albuquerque, NM 87120. (505) 897-4397.

April 23—**The Annual OB/GYN Advances in Patient Care Meeting.** Albuquerque. Thursday. Four Seasons Motor Inn. $100.00, 6 credit hours. Contact: UNM School of Medicine, CME Office, Albuquerque, NM 87131. (505) 277-3942.

May 6-8—**New Mexico Medical Society Annual Meeting.** Albuquerque. Wednesday-Friday. Albuquerque Hilton Inn. Contact: Ralph R. Marshall, Executive Director, NMMS, 2650 Yale SE, Albuquerque, NM 87106. (505) 247-0539.

May 8-10—**American College of OB/GYN Free Standing Postgraduate Course.** Albuquerque. Friday-Sunday. Albuquerque Hilton Inn. Hour for hour credit. Contact: ACOG, One East Wacker Drive, Chicago, IL 60601. (312) 222-1600.

May 15-16—**Pediatric Cardio-Pulmonary Update Symposium.** Albuquerque. Friday-Saturday. Convention Center. 10 credit hours. Contact: Steven Yabek, MD, Intermountain Pediatric Cardiology Society, UNM School of Medicine, Department of Pediatrics, Albuquerque, NM 87131. (505) 277-4361.

OREGON

This bulletin of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

University of Oregon Medical School, Department of Psychiatry, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, University of Oregon Medical School. Contact: Dept. of Psychiatry, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8144.

University of Oregon Medical School, Department of Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, University of Oregon Medical School. Contact: Dept. of Medicine, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8607.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, OR 97213. (503) 234-8211.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00-9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee, P.O. Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

EMERGENCY MEDICINE

June 4-6—**Update: Emergency Medicine.** Sponsored by the Oregon Chapter of ACEP, EDNA and OSEMTA. Thursday-Saturday. Salishan Lodge, Gleneden Beach, Oregon. For additional information please contact: Vivian Curry, c/o E/PCP Program, Good Samaritan Hospital & Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7711.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center, Portland. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-7590.

OBSTETRICS AND GYNECOLOGY

October 1-3—**Pacific Northwest Review of Obstetrics & Gynecology.** Thursday-Saturday. Thunderbird-Jantzen Beach, Portland, Oregon. For additional information please contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, Portland, OR 97201. (503) 226-1555.

INTEREST TO ALL PHYSICIANS

April 2-3—**Current Concepts in Drug Therapy.** Portland. Thursday-Friday. Jantzen Beach Thunderbird. For additional information please contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, Portland, OR 97201. (503) 225-8700.

April 8-10—**School of Medicine Alumni Association Scientific Sessions and Sommer Memorial Lectures.** Univetsity of Oregon Health Sciences Center Campus. For additional information please contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, Portland, OR 97201. (503) 225-8700.

September 11-12—**Ashland Conference: Gastroenterology.** Friday-Saturday. Ashland Hills Inn, Ashland, Oregon. For additional information please contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, Portland, OR 97201. (503) 226-1555.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. Please send information to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle 98121; or phone (206) 623-4801.

March 12-13—**Tacoma Academy of Internal Medicine.** Tacoma. Thursday-Friday. Contact: CME Pierce County.

March 16—**Gyn Oncology—Univ. of Wash. OB/GYN Sessions** (Spokane). Tuesday. 12-1 p.m., Sacred Heart Medical Center. Contact: Wm. Harvey Frazier, MD, West 101 8th Ave., Spokane, WA 99204. (509) 838-8347.

March 17—**Epilepsy.** Sacred Heart Med. Ctr. Spokane. Tuesday. Contact U/W School of Medicine.

March 19-21—**Pediatric Rehabilitation.** Thursday-Saturday. Mary Bridge Childrens' Hospital. Tacoma. Contact: CME Pierce County.

March 23—**Pain—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

March 23-27—**Advances in Family Practice.** Seattle. Monday-Friday. Contact: U/W School of Medicine.

March 26-28—**National Health Service Corps.** Seattle University. Seattle. Thursday-Saturday. Contact: U/W School of Medicine.

March 30—**Diabetes.** Seattle. Monday. Northwest Hospital. Contact: Marilyn Carlson, Northwest Hospital Education and Training Department, 1551 N 120th, Seattle, WA 98133. (206) 364-0500 ex. 1737.

March 30-April 10—**Rehabilitation Medicine Review.** Seattle. Monday-Friday. Contact: U/W School of Medicine.

April 1-4—**North Pacific Society of Neurology & Psychiatry Annual Scientific Program.** Washington Plaza Hotel. Seattle. Wednesday-Saturday. Contact: Robert B. Aigner, MD, The Polyclinic, 1200 Harvard Avenue, Seattle, WA 98122. (206) 329-1760.

April 1, 8, 15 & 29—**Medicine & Society In History.** U/W Waterfront Activities Center. Seattle. Wednesdays. 5:30-9:00 p.m. Contact: U/W School of Medicine.

April 3—**Nutrition in the Hospitalized Patient.** Seattle. Friday. Contact: U/W School of Medicine.

April 4—**Mason Clinic Day.** Seattle. Saturday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

April 4-11—**Current Concepts in OB/GYN.** Kona, Hawaii. Saturday-Saturday. U/W at Kona Surf, Kona, Hawaii. Contact: U/W School of Medicine.

April 11-18—**Office Management of Chronic Pain.** Maui, Hawaii. Saturday-Saturday. U/W at Wailea Beach, Wailea, Maui, Hawaii. Contact: U/W School of Medicine.

April 11-18—**Drug Therapy.** Maui, Hawaii. Saturday-Saturday. U/W at Royal Lahaina, Maui, Hawaii. Contact: U/W School of Medicine.

April 14—**Pediatric Psychiatry—Univ. of Wash. Pediatrics Sessions** (Spokane). Tuesday. 12-1 p.m., Sacred Heart Medical Center. Contact: Frank Reynolds, MD, WAMI Office, 3 North, Sacred Heart Medical Center, Spokane, WA 99204. (509) 455-8220.

COURSE SPONSORS AND CONTACT INFORMATION

CME PIERCE COUNTY—Contact: Mrs. Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON) — Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Sandra McDonald, Division of Continuing Medical Education, Virginia Mason Medical Center, 1100 Ninth Avenue, Seattle, WA 98101. (206) 223-6898.

April 18—**The Medical Consequences of Nuclear Weapons & Nuclear War.** U/W Meany Hall. Seattle. Saturday. Contact: U/W School of Medicine.

April 18-25—**Emergency Medical Care.** Maui, Hawaii. Saturday-Saturday. U/W at Wailea Beach, Maui, Hawaii. Contact: U/W School of Medicine.

April 27—**Total Parenteral Nutrition—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

April 30-May 2—**Trauma.** Seattle. Thursday-Saturday. Contact: U/W School of Medicine.

May 1—**Management of Acute Medical Problems.** Seattle. Friday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

May 6—**Medicine & Society in History.** U/W Waterfront Activities Center. Seattle. Wednesdays. 5:30-9:00 p.m. Contact: U/W School of Medicine.

May 7-8—**Medical Genetics and Teratology.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

May 8-9—**Washington Academy of Family Physicians Annual Scientific Program.** Yakima. Friday-Saturday. Yakima Convention Center. Contact: Carolyn Palmer, 3700 140th Avenue NE, Bellevue, WA 98005. (206) 883-8852.

May 15-16—**Medical Applications of Real-Time Ultrasound.** Seattle. Friday-Saturday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

May 15—**Medical Alumni: Medicine, Mankind and the Mountain.** Seattle. Friday. Contact: U/W School of Medicine.

May 18—**Arrhythmias—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

May 19—**Evaluation and Treatment of Premature Labor—Univ. of Wash. OB/GYN Sessions.** (Spokane). Tuesday. 12-1 p.m., Sacred Heart Medical Center. Contact: Wm. Harvey Frazier, MD, West 101 8th Ave., Spokane, WA 99204. (509) 838-8347.

May 22-23—**Northwest Academy of Otolaryngology and Head and Neck Surgery Annual Scientific Program.** Seattle. Friday-Saturday. Washington Athletic Club. Contact: C. Thomas Yarington, MD, The Mason Clinic, 1100 Ninth Avenue, Seattle, WA 98101. (206) 223-6833.

May 22-24—**Comprehensive Care for Physically Disabled Children.** Seattle. Friday-Sunday. Washington Plaza. Contact: John A. Hinckley, AACPDM, PO Box 11083, Richmond, VA 23230. (804) 355-0147.

May 23-30—**Allergy and Immunology.** Maui, Hawaii. Saturday-Saturday. U/W at Wailea Beach, Maui, Hawaii. Contact: U/W School of Medicine.

June 4-5—**Pacific Northwest Chapter of the American College of Chest Physicians: Cardiopulmonary Symposium.** Seattle. Thursday-Friday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

June 9—**Pediatric Allergy—Univ. of Wash. Pediatrics Sessions** (Spokane). Tuesday. 12-1 p.m., Sacred Heart Medical Center. Contact: Frank Reynolds, MD, WAMI Office, 3 North, Sacred Heart Medical Center, Spokane, WA 99204. (509) 455-8220.

June 11-12—**Regional Anesthesia and Nerve Block.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

(Continued on Page 53)

THE HOSPITAL of the GOOD SAMARITAN Los Angeles

presents

Plasma
Leucocyte
Platelet
Erythrocyte
Lymphocyte

APHERESIS

WEDNESDAY

APRIL 8, 1981

The Hospital of the Good Samaritan Auditorium, 634 So. Lucas Ave., Los Angeles, CA 90017

Distinguished Faculty

WAYNE A. BORDER, MD ..... *Torrance, CA*
PETER C. DAU, MD ..... *San Francisco, CA*
JEANE P. HESTER, MD ..... *Houston, TX*
HARVEY G. KLEIN, MD ..... *Bethesda, MD*
DANIEL J. WALLACE, MD ..... *Los Angeles, CA*

Course Director: JIM S. BONORRIS, MD

Fees: $40 General Admission, including luncheon

This course is acceptable for up to 6 hours Category 1 Credit towards the CMA and AMA certificates in Continuing Medical Education.

Registration for "Apheresis Symposium" April 8, 1981

Name _____

Specialty _____ Phone _____

Address _____

City _____ Zip _____

Mail check payable to: APHERESIS SYMPOSIUM

Mail check and registration form to:
APHERESIS SYMPOSIUM
Hospital of the Good Samaritan
616 So. Witmer St.
Los Angeles, CA 90017

For more information, contact:
MARY JANE THOMPSON
Coordinator of Symposia
(213) 977-2345

SUBSCRIPTION ORDER BLANK

To Receive

THE WESTERN Journal of Medicine

or to Give it as a Gift,

Return this coupon.

Please mail this coupon with enclosed payment to

WJ3/8

THE WESTERN
Journal of Medicine

731 Market Street, San Francisco, California 94103

Subscriptions (U.S. and Canada) $10 Foreign subscriptions $18

Enclosed is $_____ to cover _____ subscriptions. Subscription renewal ☐

Send subscription

TO: _____

_____
Street

_____
City State Zip

_____
Type of practice

Gift Card to read "From _____"

Regular subscription ☐ Foreign subscription ☐

TO: _____

_____
Street

_____
City State Zip

_____
Type of practice

Gift Card to read "From _____"

Regular subscription ☐ Foreign subscription ☐

Please allow six weeks for subscriptions to begin

(Continued from Page 51)

une 15-19—**Death Investigation.** Seattle. Monday-Friday. Contact: U/W School of Medicine.

une 15—**Antibiotic Update.** Sacred Heart Medical Center. Spokane. Monday. Contact: U/W School of Medicine.

une 16—**Antibiotic Update.** U/W Health Sciences Building. Seattle. Tuesday. Contact: U/W School of Medicine.

une 18-19—**Respiratory Care.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

une 18-20—**Modern Office Procedures: Minor Surgeries.** Seattle. Thursday-Saturday. Contact: U/W School of Medicine.

une 22—**Ophthalmology for the Internist—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

uly 19-27—**Alaska Cruise: OB/GYN.** Sunday-Monday. Contact: U/W School of Medicine.

uly 25-26—**Washington State Society of Anesthesiologists: Seafair III Anesthesia Meeting.** Seattle. Saturday-Sunday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

uly 27-31—**Psychiatry & The Behavioral Sciences: The 1980s.** Bayshore Inn. Vancouver, British Columbia. Monday-Wednesday and Friday. Contact: U/W School of Medicine.

August 5-7—**Great Debates in Otolaryngology.** Seattle. Wednesday-Friday. Contact: U/W School of Medicine.

August 21-28—**Alaska Cruise: Radiology.** Friday-Friday. Contact: U/W School of Medicine.

August 21-28—**Alaska Cruise: Strabismus.** Friday-Friday. Contact: U/W School of Medicine.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the Academy for Continuing Medical Education, a foundation of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Academy for Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the Academy at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the Academy for current details.

GRAND ROUNDS

SPONSOR: Primary Children's Medical Center
TITLE: **Pediatric Grand Rounds**
LOCATION: PCMC
DATE: First and third Thursdays—8:00 a.m.
CONTACT: Cathy Van Komen (801) 363-1221

SPONSOR: Utah Valley Hospital, Provo
TITLE: **Interdepartmental Grand Rounds**
LOCATION: UVH
CONTACT: Gary Watts, MD (801) 373-7850 (Ext. 2143)

* * *

March 7-14

SPONSOR: University of Utah
TITLE: **Medical and Surgical Advances in Gastroenterology**
LOCATION: Snowbird
FEE: To be announced
CREDIT: 25 hours
CONTACT: Malcolm Berenson, MD (801) 581-7802

March 14-21

SPONSOR: University of Utah
TITLE: **3rd Annual Park City Radiology Conference: Neuroradiology**
LOCATION: Park City
FEE: $240.00
CREDIT: To be announced
CONTACT: P. Ruben Koehler, MD (801) 581-8818

April 1

SPONSOR: University of Utah, Dept. of Internal Medicine
TITLE: **Clinical Pharmacology**
LOCATION: UUMC
FEE: None
CREDIT: 2 hours
CONTACT: Malcolm Berenson, MD (801) 581-7803

April 6-8

SPONSOR: University of Utah
TITLE: **Clinico-pathologic Approach to Urinary Sediment**
LOCATION: Hotel Utah, Salt Lake City
FEE: To be announced
CREDIT: 18.5 hours
CONTACT: G. Berry Schumann, MD (801) 581-5959

SPONSORS OF COURSES—ABBREVIATIONS

AF: Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.
CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.
CWH: Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461
FHP: Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.
HAFB: Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.
LDSH: Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.
MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.
OEH: Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.
OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409
PCMC: Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.
SHCC: Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.
SLSC: Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.
UAFP: Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.
UUMC: University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.
UVH: Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.
VAMC: Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—4107 Laurel St., Anchorage 99504. Annual Meeting: May 23-27, 1981, Glacier Bay Lodge, Glacier Bay.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. Annual Meeting: May 20-24, 1981, The Pointe Resort, Phoenix.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: March 13-18, 1981, Disneyland Hotel, Anaheim.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. Annual Meeting: September 9-12, 1981, Keystone.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. Annual Meeting: October 12-16, 1981, Ilikai Hotel, Honolulu.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. Annual Meeting: July 23-26, 1981, Sun Valley.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Interim Meeting: April 10-11, 1981, Colonial Inn, Helena. Annual Meeting: October 1-3, 1981, Copper King Inn, Butte.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. Annual Meeting: May 15-17, 1981, Carson City.

New Mexico Medical Society—2650 Yale SE, Albuquerque 87106. Annual Meeting: May 6-8, 1981, Hilton Inn, Albuquerque.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. Annual Scientific Session: October 29-30, 1981, Portland.

Utah State Medical Association—540 East Fifth South St., Salt Lake City 84102. Annual Meeting: September 8-11, 1981, Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. Annual Meeting: September 24-27, 1981, Davenport Hotel, Spokane.

Wyoming State Medical Society—P.O. Drawer 4009, Cheyenne 82001. Annual Meeting: June 22-26, 1981, Ramada Snow King Inn, Jackson.

April 8-10

SPONSOR: University of Utah Rocky Mountain Center for Occupational and Environmental Health/ University of Arizona Center for Occupational Safety and Health/University of Texas Health Science Center, School of Public Health
TITLE: **3rd Annual Park City Environmental Health Conference: Legal and Ethical Dilemmas in Occupational Health**
LOCATION: Prospector Square Lodge, Park City
FEE: Advance registration, $195.00; after March 13, $250.00
CREDIT: 20.5 hours
CONTACT: Katharine Blosch (801) 581-5710

April 17

SPONSOR: Academy for Continuing Medical Education
TITLE: **First Intermountain Conference on CME**
LOCATION: TriArc Travel Lodge, Salt Lake City
FEE: $50.00 (attendance limited to 100)
CREDIT: 7 hours (certified by University of Utah College of Medicine)
CONTACT: Pam Hanson, ACME (801) 355-5290

April 27-May 5

SPONSOR: University of Utah
TITLE: **The London Knee Course**
LOCATION: London, England
FEE: To be announced
CREDIT: 26 hours
CONTACT: Kent M. Samuelson, MD (801) 581-7601

June 22-25

SPONSOR: University of Utah
TITLE: **Alcoholism and Other Drug Dependencies**
LOCATION: University Medical Center, Classroom C
FEE: To be announced
CREDIT: 28 hours
CONTACT: James R. Swenson, MD (801) 581-7985

November 6

SPONSOR: LDS Hospital
TITLE: **Postgraduate Course—Renal/Pulmonary Syndromes**
LOCATION: Hotel Utah, Salt Lake City
FEE: To be announced
CREDIT: To be announced
CONTACT: C. DuWayne Schmidt, MD (801) 350-1813

Note: Dates, times, places and programs are subject to change on occasion. Please check with the sponsoring organization or the Academy for details.

Index to
The Western Journal of Medicine Advertising

AMERICAN HOLISTIC MEDICAL INSTITUTE
8th Scientific Meeting 30
AUTOMATED SERVICES 41
AYERST LABORATORIES
Premarin 18, 19, 20
BANK OF AMERICA
Business Services 11
BANKERS INVESTMENT COMPANY/SECURITY PACIFIC FINANCE CORP. 25
BRIG COMPUTERS AND SOFTWARE 5
BRISTOL LABORATORIES
Tygopen 28, 29, 30
BURROUGHS WELLCOME CO.
Empirin c Codeine 23
Neosporin Topical 3
CLASSIFIED 22, 24, 34, 36
DOCTORS' CO., THE 31
ELI LILLY AND COMPANY
Keflex 33
HCP CONDO RESORTS 25
HELIOSYSTEMS 13
HOSPITAL OF THE GOOD SAMARITAN, THE
Apheresis 51
INTERNATIONAL CONFERENCE
Conferences on Legal-Medical Issues 30
KEY PHARMACEUTICALS, INC.
Theo-Dur 38, 39, 40
MILLS MEMORIAL HOSPITAL AND SOCIETY OF ORTHOPAEDIC MEDICINE
Cyriax on Orthopedic Medicine 35
PRITIKIN LONGEVITY CENTER 37
ROCHE LABORATORIES
Bactrim ..... 2nd Cover, 1, 2
Limbitrol 46, 47, 48
Valium ..... 3rd and 4th cover
SEQUOIA GROUP INCORPORATED 26, 27
SMITH, KLINE & FRENCH CO.
Dyazide 32
E. R. SQUIBB & SONS INC.
Corgard 7, 8, 9, 10
UNIVERSITY OF CALIFORNIA/IRVINE
Campus Personnel 25
UNIVERSITY OF CALIFORNIA/IRVINE DIV. OF ORTHOPEDIC SURGERY
Sports Medicine for the 80's; Financial Planning for the 80's . 40
WYETH LABORATORIES
LO/OVRA 14, 15, 16

THE WESTERN Journal of Medicine

VOLUME 134 • NUMBER 4 **APRIL 1981**

283 *Extrahepatic Biliary Duct Trauma—A Spectrum of Injuries*
TODD B. BURT, MD, and JAMES A. NELSON, MD

290 *Recent Advances in Cataract Operations—Phacoemulsification, Intraocular Lens Implantation and Prolonged-Wear Soft Contact Lenses*
JAMES J. SALZ, MD

MEDICAL PROGRESS
296 *Blood Pressure in Infants, Children and Adolescents* ARTHUR J. MOSS, MD

SPECIALTY CONFERENCE
315 *Thrombosis: Its Role and Prevention in Cardiovascular Events—Part II*
Participants: LAURENCE A. HARKER, MD; ARTHUR R. THOMPSON, MD, PhD, and JOHN M. HARLAN, MD

MEDICAL STAFF CONFERENCE
333 *Newer Antiarrhythmic Drugs* Chief Discussant: DAVID S. HESS, MD

IMPORTANT ADVANCES IN CLINICAL MEDICINE
342 *Urology—Epitomes of Progress*

EDITORIALS
348 • *Welcome NMMS* • *Measuring Blood Pressure in Young Patients* • *Patients and Others as Doctors* • *From Clubbing to Collagen* • *The Changing Cigarette*

CASE REPORTS
354 *Idiopathic Hypertrophic Osteoarthropathy (Pachydermoperiostosis)*
DAVID A. HERBERT, MD, and W. JEFFREY FESSEL, MD

357 *Retroperitoneal Fibrosis as a Cause of Fever of Undetermined Origin*
CDR WILLIAM E. BYRD, MC, USN; LCDR ROBERT E. HUNT, MC, USN, and LCDR RICHARD BURGESS, MC, USN

361 *Treatment of Agenesis of the Diaphragm and Esophageal Crura—An 18-Year Follow-up*
J. ORDIE SHAFFER, MD

CORRESPONDENCE
364 • *Infirmaries: A Way to Reduce Medical Costs?* • *Therapy for Ankylosing Spondylitis* • *Diet Not Shown Effective in Psoriasis* • *Laboratory Evaluation of Neurosyphilis* • *The Prevention of Nuclear War as a Medical Priority* • *HAFE in Nepal* • *Hypophosphatemia: Correct Quantity of 50 Percent Magnesium Sulfate; With Reply by Author*

FROM A MEDICAL STUDENT
367 *Preventive Medicine in Practice: The State of the Art* DAVID J. MARON, BA

376 *In Memoriam*

378 *Subscription Information*

Detailed Table of Contents, See Advertising Pages 7 and 11

Information for Authors, See January Issue, Advertising Page 10

★ **CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA, HAWAII AND NEVADA; ALASKA, MONTANA AND IDAHO; NEW MEXICO; OREGON; WASHINGTON; UTAH**
(See Advertising Page 15)

★★ **Official Journal of the California Medical Association, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association and the Washington State Medical Association**

UNPARALLELED PROOF OF NIGHT-LONG EFFICACY

ONLY DALMANE® C IV

flurazepam HCl/Roche

IS SIGNIFICANTLY EFFECTIVE AGAINST THE MAJOR FORMS OF INSOMNIA WITH NO WORSENING OF SLEEP ON DISCONTINUATION

Because subjective reports of insomnia and subsequent experience with sleep medication do not adequately substantiate either the validity of the complaints or the efficacy of medication, the sleep laboratory has become a valuable tool to do both. It is here that Dalmane has been objectively tested and proven effective.

Patients with objectively validated insomnia—difficulty in falling asleep, staying asleep, or both—received Dalmane 30 mg for up to 28 consecutive nights with no increase in dosage and no significant decrease in efficacy. And, upon discontinuation of Dalmane, there was no worsening of sleep past baseline levels on any parameter.[1-3]

Since insomnia is often transient, therapy for as long as 4 weeks should be given only after careful assessment of patient need with special attention to periodic blood counts and liver and kidney function tests.

Advise patients who ingest alcoholic beverages or other CNS depressants against doing so while on Dalmane therapy.

Patients should also be cautioned against engaging in hazardous occupations requiring mental alertness, such as operating machinery or driving a motor vehicle after ingesting the drug.

OM THE START
ep within 17 minutes,
average[4]
THROUGH THE NIGHT
With fewer awakenings[4]
AWAKENING
er a 7 to 8 hour sleep,
average[4]
ROCHE
Please see summary of product information on the following page.

THE STANDARD FOR HYPNOTIC EFFICACY WITH IMPORTANT ADDED BENEFITS

- Well tolerated[4]
- Does not significantly influence the results of many commonly ordered laboratory tests, including triglycerides, uric acid, glucose, SGOT, alkaline phosphatase and total protein[5,6] (See adverse reactions section of complete product information.)
- Compatible with chronic warfarin therapy; no unacceptable fluctuation in prothrombin time reported[7,8]

UNLIKE NONSPECIFIC MEDICATIONS USED FOR SLEEP

Tricyclic antidepressants

–which are *not* sleep specific,[9] yet are sometimes used in nondepressed patients for sleep

–which can cause transient insomnia in the elderly[10]

–which can require careful monitoring in cardiovascular patients[10]

–which have strong anticholinergic effects[10]

Antihistamines

–which are *not* reliable sleep-inducing agents[11]

–which may produce stimulation instead[11]

–which have anticholinergic effects[11]

Major tranquilizers

–whose side effects may be troublesome for nonpsychotic patients[12]

–where tolerance for sedation appears rapidly[12]

Dalmane (flurazepam HCl/Roche) does not cause worsening of sleep beyond baseline levels upon discontinuation.[13]

EFFECTIVE ALL NIGHT SLEEP-SPECIFIC

DALMANE® (C IV)

flurazepam HCl/Roche

One 15-mg capsule *h.s.*–recommended initial dosage for elderly or debilitated patients.
One 30-mg capsule *h.s.*–usual adult dosage
(15 mg may suffice in some patients).

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; in acute or chronic medical situations requiring restful sleep. Objective sleep laboratory data have shown effectiveness for at least 28 consecutive nights of administration. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended.

Contraindications: Known hypersensitivity to flurazepam HCl.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).

Usage in Pregnancy: **Several studies of minor tranquilizers (chlordiazepoxide, diazepam, and meprobamate) suggest increased risk of congenital malformations during the first trimester of pregnancy. Dalmane (flurazepam HCl/Roche), a benzodiazepine, has not been studied adequately to determine whether it may be associated with such an increased risk. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated patients, it is recommended that the dosage be limited to 15 mg to reduce risk of oversedation, dizziness, confusion and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies, or with impaired renal or hepatic function. Periodic blood counts and liver and kidney function tests are advised during repeated therapy.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity, and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase.

Dosage: Individualize for maximum beneficial effect.
Adults: 30 mg usual dosage; 15 mg may suffice in some patients.
Elderly or debilitated patients: 15 mg recommended initially until response is determined.

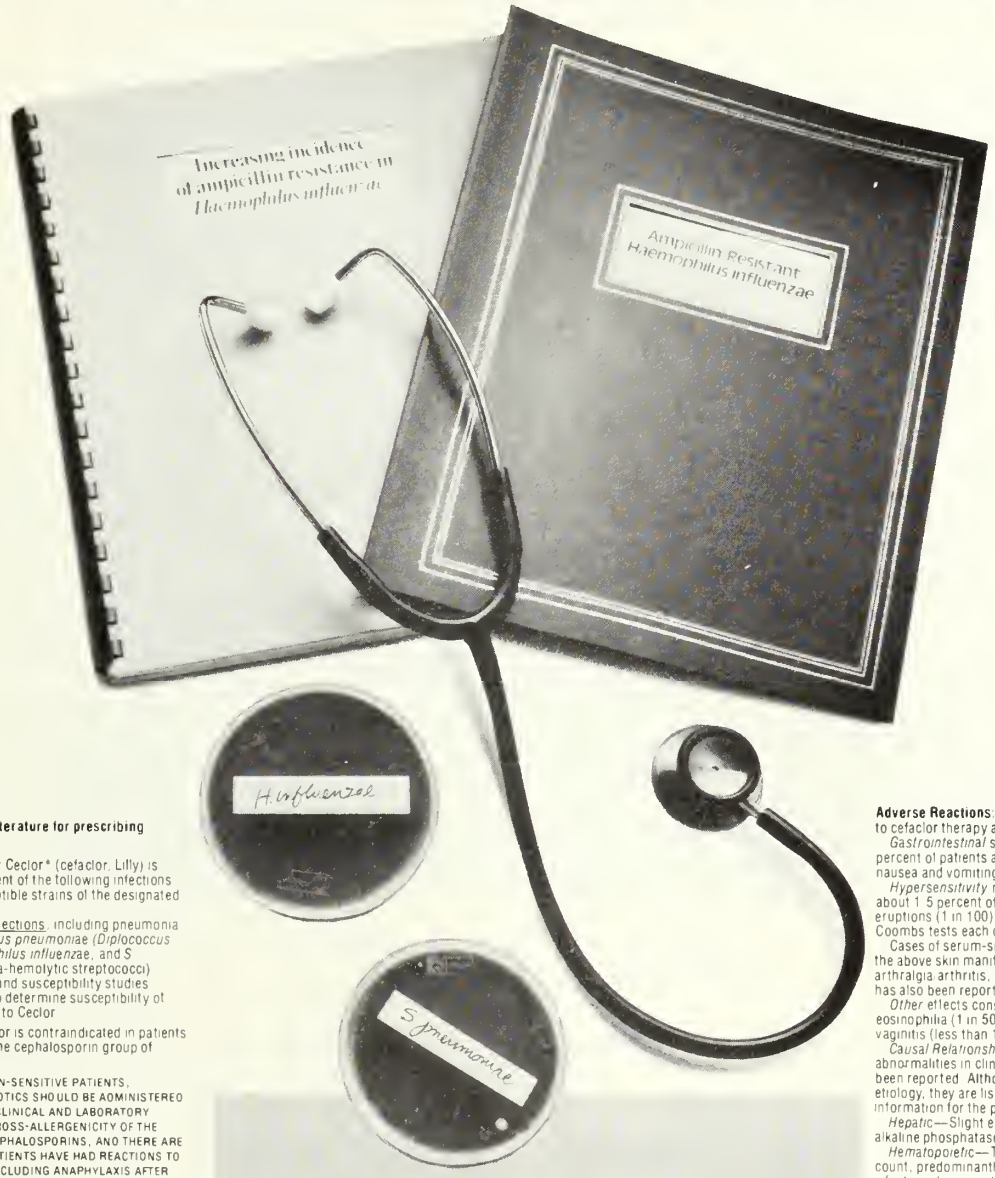
Supplied: Capsules containing 15 mg or 30 mg flurazepam HCl.

References: 1. Kales A, *et al: Clin Pharmacol Ther 19*:576-583, May 1976 **2.** Dement WC, *et al: Behav Med 5*:25-31, Oct 1978 **3.** Kales A, *et al: Clin Pharmacol Ther 18*:356-363, Sep 1975 **4.** Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ **5.** Moore JD, Weissman L: *J Clin Pharmacol 16*:241-244, May-Jun 1976 **6.** Spiegel HE: Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ **7.** Robinson DS, Amidon EL: Interaction of benzodiazepines with warfarin in man, in *The Benzodiazepines*, edited by Garattini S, Mussini E, Randall LO. New York, Raven Press, 1973, pp. 641-646 **8.** Warfarin Study: Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ **9.** Baldessarini RJ: Drugs and the treatment of psychiatric disorders, chap. 19, in Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, ed 6. New York, Macmillan Publishing Co. Inc., 1980, pp. 391-447 **10.** Cole JO, Davis JM: Antidepressant drugs, chap. 31.2, in *Comprehensive Textbook of Psychiatry/II*, edited by Freedman AM, Kaplan HI, Sadock BJ, ed 2. Baltimore, The Williams & Wilkins Company, vol 2, 1976, pp. 1941-1956 **11.** Douglas WW: Histamine and 5-hydroxytryptamine (serotonin) and their antagonists, chap. 26, in Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, ed 6. New York, Macmillan Publishing Co. Inc., 1980, pp. 609-646 **12.** Davis JM, Cole JO: Antipsychotic drugs, chap. 31.1, in *Comprehensive Textbook of Psychiatry/II*, edited by Freedman AM, Kaplan HI, Sadock BJ, ed 2. Baltimore, The Williams & Wilkins Company, vol 2, 1976, pp. 1921-1940 **13.** Kales A, *et al: JAMA 241*:1692-1695, Apr 20, 1979

ROCHE®

ROCHE PRODUCTS INC.
Manati, Puerto Rico 00701

An added complication... in the treatment of bacterial bronchitis*



Some ampicillin-resistant strains of Haemophilus influenzae—a recognized complication of bacterial bronchitis*—are sensitive to treatment with Ceclor.[1-6]

In clinical trials, patients with bacterial bronchitis due to susceptible strains of Streptococcus pneumoniae, H. influenzae, S. pyogenes (group A beta-hemolytic streptococci), or multiple organisms achieved a satisfactory clinical response with Ceclor.[7]

Ceclor®
cefaclor
Pulvules®, 250 and 500 mg

*Many authorities attribute acute infectious exacerbation of chronic bronchitis to either *S. pneumoniae* or *H. influenzae*.*

Note: Ceclor® (cefaclor) is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

References

1. Antimicrob. Agents Chemother., *8*: 91, 1975
2. Antimicrob. Agents Chemother., *11*: 470, 1977
3. Antimicrob. Agents Chemother., *13*: 584, 1978
4. Antimicrob. Agents Chemother., *12*: 490, 1977
5. Current Chemotherapy (edited by W. Siegenthaler and R. Luthy), II: 880. Washington, D.C.: American Society for Microbiology, 1978
6. Antimicrob. Agents Chemother., *13*: 861, 1978
7. Data on file, Eli Lilly and Company
8. Principles and Practice of Infectious Diseases (edited by G.L. Mandell, R.G. Douglas, Jr. and J.E. Bennett), p. 487. New York: John Wiley & Sons, 1979

Additional information available to the profession on request from Eli Lilly and Company, Indianapolis, Indiana 46285

Lilly

Eli Lilly Industries, Inc.
Carolina, Puerto Rico 00630

100061

ef Summary
nsult the package literature for prescribing ormation.

ications and Usage: Ceclor® (cefaclor, Lilly) is cated in the treatment of the following infections en caused by susceptible strains of the designated roorganisms:
lower respiratory infections, including pneumonia sed by *Streptococcus pneumoniae* (*Diplococcus umoniae*), *Haemophilus influenzae*, and *S. ogenes* (group A beta-hemolytic streptococci) ppropriate culture and susceptibility studies uld be performed to determine susceptibility of causative organism to Ceclor.

traindication: Ceclor is contraindicated in patients h known allergy to the cephalosporin group of biotics.

rnings: IN PENICILLIN-SENSITIVE PATIENTS, CHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED OUSLY. THERE IS CLINICAL AND LABORATORY IDENCE OF PARTIAL CROSS-ALLERGENICITY OF PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE STANCES IN WHICH PATIENTS HAVE HAD REACTIONS TO H DRUG CLASSES (INCLUDING ANAPHYLAXIS AFTER RENTERAL USE).
ntibiotics, including Ceclor, should be administered ously to any patient who has demonstrated some n of allergy, particularly to drugs.

cautions: If an allergic reaction to cefaclor occurs, drug should be discontinued, and, if necessary, the ent should be treated with appropriate agents, e.g., ssor amines, antihistamines, or corticosteroids. rolonged use of cefaclor may result in the growth of nonsusceptible organisms. Careful rvation of the patient is essential. If superinfection urs during therapy, appropriate measures should taken.
positive direct Coombs tests have been reported ring treatment with the cephalosporin antibiotics. In matologic studies or in transfusion cross-matching cedures when antiglobulin tests are performed on minor side or in Coombs testing of newborns ose mothers have received cephalosporin antibiotics re parturition, it should be recognized that a itive Coombs test may be due to the drug. eclor should be administered with caution in the ence of markedly impaired renal function. Under s a condition, careful clinical observation and oratory studies should be made because safe age may be lower than that usually recommended s a result of administration of Ceclor, a false-itive reaction for glucose in the urine may occur. T has been observed with Benedict's and Fehling's tions and also with Clinitest® tablets but not with Tape® (Glucose Enzymatic Test Strip, USP, Lilly).
sage *in Pregnancy*—Although no teratogenic or fertility effects were seen in reproduction studies ice and rats receiving up to 12 times the imum human dose or in ferrets given three times maximum human dose, the safety of this drug for in human pregnancy has not been established. T benefits of the drug in pregnant women should eighed against a possible risk to the fetus.
sage *in Infancy*—Safety of this product for use in nts less than one month of age has not been ablished.

Adverse Reactions: Adverse effects considered related to cefaclor therapy are uncommon and are listed below.
Gastrointestinal symptoms occur in about 2.5 percent of patients and include diarrhea (1 in 70) and nausea and vomiting (1 in 90).
Hypersensitivity reactions have been reported in about 1.5 percent of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs tests each occur in less than 1 in 200 patients.
Cases of serum-sickness-like reactions, including the above skin manifestations, fever, and arthralgia/arthritis, have been reported. Anaphylaxis has also been reported.
Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients).
Causal Relationship Uncertain—Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician.
Hepatic—Slight elevations in SGOT, SGPT, or alkaline phosphatase values (1 in 40).
Hematopoietic—Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40).
Renal—Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200). [103080R]

THE WESTERN Journal of Medicine

Since 1902 (ISSN 0093-0415)

731 MARKET ST. • SAN FRANCISCO, CA 94103 • TELEPHONE (415) 777-2000

Official Journal of the California Medical Association, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association and the Washington State Medical Association

MALCOLM S. M. WATTS, MD, *Editor*
LLOYD H. SMITH, JR, MD, *Associate Editor*
DAVID GREER, *Managing Editor*
BARBARA T. ROONEY, *Assistant Managing Editor*
VAL BOSMOE, *Editorial Assistant*
MARY JANE MacDWYER, *Copy Editor*
MARY KAY COWANS, *Advertising Production Manager*
KEVIN McKINNEY, *Circulation Coordinator*

editorial communications to DR. WATTS

business communications to MR. GREER

Editorial Board

Chairman of the Board
Malcolm S. M. Watts, San Francisco, Ca

Special Editor for Idaho
E. R. W. Fox, Coeur d'Alene, Id

Special Editor for Nevada
Thomas J. Scully, Reno, Nv

Special Editor for New Mexico
Marcus J. Smith, Santa Fe, NM

Special Editor for Utah
John H. Holbrook, Salt Lake City, Ut

Special Editor for Washington
David Hopkins, Federal Way, Wa

Allergy
Harold S. Novey, Orange, Ca
Abba I. Terr, San Francisco, Ca

Anesthesiology
Ronald L. Katz, Los Angeles, Ca

Cardiac and Thoracic Surgery
John E. Connolly, Irvine, Ca
Albert Starr, Portland, Or

Chest Diseases
Roger K. Larson, Fresno, Ca
Thomas L. Petty, Denver, Co

Dermatology
John H. Epstein, San Francisco, Ca
George F. Odland, Seattle, Wa
Richard B. Stoughton, San Diego, Ca

General and Family Practice
Daniel D. Roberts, Central Point, Or
Harmon E. Holverson, Emmett, Id
Wilfred Snodgrass, Santa Monica, Ca

General Surgery
Fred M. Anderson, Reno, Nv
Daniel T. Cloud, Phoenix, Az
Paul A. Ebert, San Francisco, Ca
Lucius D. Hill, Seattle, Wa
Frank G. Moody, Salt Lake City, Ut

Industrial Medicine and Toxicology
Thomas H. Milby, Berkeley, Ca

Internal Medicine
Robert W. Burroughs, Spokane, Wa
Theodore C. Eickhoff, Denver, Co
Robert L. Hare, Portland, Or
Robert H. Moser, Philadelphia, Pa
George A. Porter, Portland, Or
Helen M. Ranney, San Diego, Ca
David D. Ulmer, Los Angeles, Ca
Edgar Wayburn, San Francisco, Ca
Ralph C. Williams, Jr, Albuquerque, NM

Neurology
Pierre M. Dreyfus, Sacramento, Ca
Philip D. Swanson, Seattle, Wa
W. C. Wiederholt, La Jolla, Ca

Neurosurgy
John R. Green, Phoenix, Az
Arthur A. Ward, Jr, Seattle, Wa
Charles B. Wilson, San Francisco, Ca

Nuclear Medicine
Joseph P. Kriss, Stanford, Ca

Obstetrics and Gynecology
Ralph C. Benson, Portland, Or
Ralph W. Hale, Honolulu, Hi
W. LeRoy Heinrichs, Stanford, Ca
Morton A. Stenchever, Seattle, Wa

Ophthalmology
Robert S. Hepler, Los Angeles, Ca
Bruce E. Spivey, San Francisco, Ca

Orthopedics
Ernest M. Burgess, Seattle, Wa
Duane M. Kline, Jr, Cheyenne, Wy

Otolaryngology
Roger Boles, San Francisco, Ca
Mansfield F. W. Smith, San Jose, Ca

Pathology
Richard L. Kempson, Stanford, Ca

Pediatrics
Louis K. Diamond, San Francisco, Ca
William L. Nyhan, San Diego, Ca
Irving Schulman, Stanford, Ca
Arnold L. Smith, Seattle, Wa

Pharmacology
George N. Aagaard, Seattle, Wa

Physical Medicine and Rehabilitation
Glenn G. Reynolds, San Jose, Ca

Plastic Surgery
Richard P. Jobe, Los Altos, Ca
N. John Wilde, Fresno, Ca

Psychiatry
Carl Eisdorfer, Seattle, Wa
Alan I. Levenson, Tucson, Az
Helen Tausend, Beverly Hills, Ca
Joe Paul Tupin, Sacramento, Ca

Public Health
J. M. Stubblebine, Greenbrae, Ca

Radiology
M. Paul Capp, Tucson, Az
Melvin M. Figley, Seattle, Wa
Marshall Rowen, Orange, Ca

Urology
Richard Middleton, Salt Lake City Ut
Thomas A. Stamey, Stanford Ca

Consulting Editor
Medical Services and Health Care
Paul J. Sanazaro, Berkeley, Ca

POLICY COMMITTEE

BRAD COHN, MD
CHARLES M. HAIR, MD
GLADDEN V. ELLIOTT, MD
SAMUEL HOROWITZ, MD
ROBERT D. BURNETT, MD
THEODORE W. LORING, MD
MALCOLM S. M. WATTS, MD

Advertisements—THE WESTERN JOURNAL OF MEDICINE is published the first week of each month. Advertising copy must be received not later than the first of the month preceding issue. Advertising rates will be sent on request. Acceptance of advertising is contingent upon approval by the Advertising Committee. The journal reserves the right to reject any advertisement.

ADVERTISING SALES REPRESENTATIVES

EAST:
SAUL HORNIK
12 COURT ST.
FREEHOLD, NJ 07728
TEL: (201) 462-8004

MIDWEST:
R. C. JOHNSON & ASSOCIATES
RICHARD C. JOHNSON
547 WEST MELROSE
CHICAGO, IL 60657
TEL: (312) 327-6969

WEST:
MEDIA SERVICES
DARIEN DeLORENZO
LYNNE JEFFES
2612 BELMONT CANYON RD.
BELMONT, CA 94002
TEL. (415) 595-2203
(415) 348-7478

CLASSIFIED:
731 MARKET ST.
SAN FRANCISCO, CA 94103
TEL. (415) 777-2000
(415) 777-0424

Copyright 1981 by the California Medical Association
Owned and Published by the California Medical Association
All material subject to this copyright appearing in THE WESTERN JOURNAL OF MEDICINE may be photocopied for the noncommercial purpose of scientific or educational advancement. Volumes begin with January and July.

The subscription price per year is $10 in the United States and Canada; $18 in all other countries. Single copies are $2. Address all subscription communications to THE WESTERN JOURNAL OF MEDICINE Circulation, 731 Market St., San Francisco, CA 94103.

Allow six weeks for subscriptions to begin. Past issues must be bought individually. So long as reserve stocks are available, missing issue requests from subscribers are honored for up to six months after the issue date. Thereafter, the single copy rate of $2.00 is applicable for each issue available.

Change of Address—Requests for change of address should give both the old and new addresses. Allow six weeks for change-over.

CONTRIBUTIONS OF SCIENTIFIC AND ORIGINAL ARTICLES

Responsibilities for Statements and Conclusions in Original Articles—Authors are responsible for all statements, conclusions and methods of presenting their subjects. These may or may not be in harmony with the views of the editorial staff. It is aimed to permit authors to have as wide latitude as the general policy of the journal and the demands on its space may permit. The right to reduce, revise or reject any manuscript is always reserved.

Exclusive Publication—Articles are accepted for publication on condition that they are contributed solely to this journal. Ordinarily contributors will be notified within 60 days if a manuscript is accepted for publication. Every effort will be made to return unused manuscripts.

"Information for Authors"—A complete guide to manuscript submission and journal style is available on request and also appears in each January and July issue.

Manuscripts—Ordinarily manuscripts should not exceed 3,000 words (less than 15 typed double-spaced pages). The *original* manuscript and two copies should be submitted, typed double-spaced throughout. If photographic illustrations are desired, three sets of clear, unmounted black and white glossy prints should be supplied. For line drawings, original artwork or glossy prints are acceptable. Tables should be typed on separate sheets of paper.

References—References should conform to the following order: name of author, title of article, name of periodical, and volume with inclusive pages, month and year—i.e., Lee GS: The heart rhythm following therapy with digitalis—In theory and practice. Arch Int Med 44:554-562, Dec 1942. They should be listed in the order in which they are cited in the text, numbered in sequence and punctuated as above.

Reprints—Reprints are available to authors at established standard rates.

"Entered as second class matter at the post office in San Francisco under the Act of March 3, 1879." Acceptable for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized August 10, 1918. Publication Number 084480.

The Talk of the '80s.

SoftCare.

A New Medical Billing System That is Easy, and Works!

FILL IN THE BLANKS

The only system that works like you do. Add, change, or delete material right on the form (displayed on the video screen). It's really easier than filling in the blank because you can go back and type over any mistake you make.

NO BATCHING

As the information is entered, the system automatically detects clerical errors in patient information, procedure codes, and procedural data. No waiting days or weeks for verification.

INSTANT ACCESS

Up to date patient information available anytime. Patient files are updated everytime a transaction is entered. All you need to check their files is to enter the patient's name — no ID number.

PRIVATE AND THIRD PARTY BILLING

System keeps track of third party billing and insurance claims. You can bill the patient on paper while they are in the office! Resubmission of a claim is as simple as pushing a button.

TECHNICAL SPECIFICATIONS

Written in Pascal, the system runs on most any 56K or 64K micro or mini computer. The system is currently operating on Dynabyte, Cromemco, Onyx, Vector Graphic, and Digital Equipment Corporation (DEC) computers. Different systems provide 500 to 10,000+ patient capacity.

Contact your Local computer store or

PBS PROFESSIONAL BUSINESS SOFTWARE

119 Fremont Street, San Francisco, CA 94105, (415) 546-1596

Commitment.

It is evident in a doctor's every action. Commitment. It is the key to professional excellence. In the medical field. And in ours.

At Insurance Corporation of America our commitment has always been to a single goal: To provide physicians with the finest professional liability insurance.

Over the years ICA has consistently offered the strongest possible coverage combined with the highest standard of professional service. Our specialization, conservative management, and commitment in this one field have enabled us to achieve excellence within the industry.

For further information, contact: Insurance Corporation of America, ICA Center 4295 San Felipe, Box 56308, Houston, Texas 77027. 1-800-231-2651. In Texas call 1-800-392-9702 (Check for availability in your state.)

ICA **PROFESSIONAL LIABILITY INSURANCE.**

WE'RE THE SPECIALIST IN THE FIELD.

THE WESTERN

Journal of Medicine

VOLUME 134 • NUMBER 4 **APRIL 1981**

TABLE OF CONTENTS

283 *Extrahepatic Biliary Duct Trauma—A Spectrum of Injuries*
TODD B. BURT, MD, and JAMES A. NELSON, MD
From the Department of Radiology, University of Utah College of Medicine, Salt Lake City.

290 *Recent Advances in Cataract Operations—Phacoemulsification, Intraocular Lens Implantation and Prolonged-Wear Soft Contact Lenses*
JAMES J. SALZ, MD
From the Department of Ophthalmology, Los Angeles County/University of Southern California Medical Center, Los Angeles.

296 *Blood Pressure in Infants, Children and Adolescents* ARTHUR J. MOSS, MD
From the Department of Pediatrics, UCLA School of Medicine, Center for the Health Sciences, Los Angeles.

315 *Thrombosis: Its Role and Prevention in Cardiovascular Events—Part II*
Participants: LAURENCE A. HARKER, MD; ARTHUR R. THOMPSON, MD, PhD, and JOHN M. HARLAN, MD
An edited transcription of a Hematology-Oncology Conference, Division of Hematology, Department of Medicine, University of Washington School of Medicine, Seattle.

333 *Newer Antiarrhythmic Drugs* Chief Discussant: DAVID S. HESS, MD
A discussion selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from a transcription, it was prepared by Drs. David W. Martin, Jr, Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine.

Urology—Epitomes of Progress
Items of progress in urology. Each item in the judgment of a panel of knowledgeable physicians has recently become reasonably firmly established, both as to scientific fact and important clinical significance.

342 *Diagnostic Fine-Needle Aspiration* JEFFREY J. POLLEN, MD

342 *Ultrasonography in Evaluation of the Scrotum* DANIEL NACHTSHEIM, MD

343 *Detection of Nonpalpable Varicoceles* C. LOWELL PARSONS, MD

343 *Oxalate Stone Disease After Jejunoileal Bypass Operations* SAKTI DAS, MD

344 *Electron Microscopy for Detecting Changes in Undescended Testes* GEORGE W. KAPLAN, MD

344 *Antegrade Pyelography and Percutaneous Nephrostomy* JOSEPH D. SCHMIDT, MD

345 *Serum Markers for Detecting Testicular Tumors* DANIEL A. NACHTSHEIM, MD

345 *Immediate Versus Delayed Endocrine Therapy for Prostatic Carcinoma*
ROGER BARNES, MD; HENRY HADLEY, MD, and R. T. BERGMAN, MD

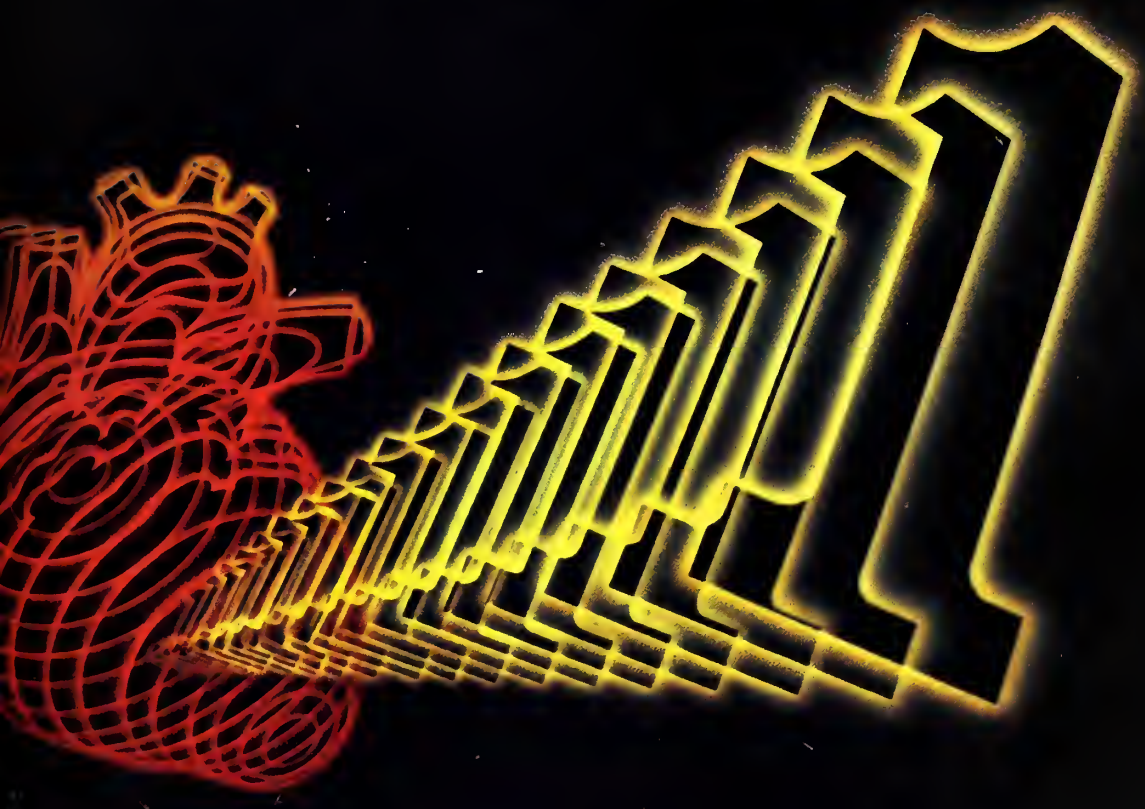
346 *Abdominal Staging Methods for Study of Testicular Tumors* RICHARD D. WILLIAMS, MD

346 *Detection of Specific Prostatic Acid Phosphatase* DANIEL A. NACHTSHEIM, MD

(Continued on Page 11)

Only one beta-blocker provides once-a-day round-the-clock protection in both hypertension and angina pectoris.

CORGARD®
[nadolol tablets]
IS THE ONE



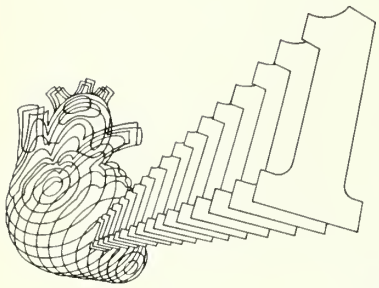
Reliable 24-hour beta blockade at all titrated dosages

SQUIBB®

Innovators in cardiovascular medicine

See next page for brief summary.

The only once-a-day beta-blocker for both hypertension and angina pectoris



CORGARD®
nadolol tablets

40 mg, 80 mg, 120 mg, 160 mg scored tablets

CORGARD® TABLETS
Nadolol Tablets

DESCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery — Because beta-blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** — Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory** — Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** — Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System** — reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal** — mesenteric arterial thrombosis; ischemic colitis. **Hematologic** — agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic** — fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous** — reversible alopecia; Peyronie's disease; erythematous rash.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm — Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to 1(mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval — see package insert for dosage in these patients.

For full prescribing information, consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and 1000 tablets and in Unimatic® single-dose packs of 100 tablets.

SQUIBB®

©1981 E.R. Squibb & Sons, Inc. Issued: March 1981 511-518

(Continued from Page 7)

348 *Welcome NMMS*

348 *Measuring Blood Pressure in Young Patients* SHEILA C. MITCHELL, MD
Dr. Mitchell, now of Princeton, New Jersey, has served with the National Heart, Lung, and Blood Institute, Bethesda, Maryland.

350 *Patients and Others as Doctors*

352 *From Clubbing to Collagen* ROBERT C. SIEGEL, MD
Dr. Siegel is Associate Clinical Professor of Medicine and Orthopedics, University of California, San Francisco, School of Medicine.

353 *The Changing Cigarette* JOHN H HOLBROOK, MD
Dr. Holbrook is Associate Professor, Department of Internal Medicine, University of Utah Medical Center, and Special Editor for Utah, Salt Lake City.

354 *Idiopathic Hypertrophic Osteoarthropathy (Pachydermoperiostosis)*
DAVID A. HERBERT, MD, and W. JEFFREY FESSEL, MD
From the Department of Medicine, Kaiser-Permanente Medical Center, Los Angeles, and the Department of Medicine, Kaiser-Permanente Medical Center, San Francisco.

357 *Retroperitoneal Fibrosis as a Cause of Fever of Undetermined Origin*
CDR WILLIAM E BYRD, MC, USN; LCDR ROBERT E HUNT, MC, USN, and LCDR RICHARD BURGESS, MC, USN
From the Divisions of Rheumatology and Pathology, Naval Regional Medical Center, Portsmouth, Virginia.

361 *Treatment of Agenesis of the Diaphragm and Esophageal Crura—An 18-Year Follow-up*
J. ORDIE SHAFFER, MD
This article is adapted from a paper presented to the Chinese Medical Association at Wuhan, China, October 13, 1979. Dr. Shaffer is in private practice in Hayward, California.

364 *Infirmaries: A Way to Reduce Medical Costs?* ED SARGENT, MD

364 *Therapy for Ankylosing Spondylitis* RICHARD MAUN, MD

364 *Diet Not Shown Effective in Psoriasis* MARVIN RAPAPORT, MD

365 *Laboratory Evaluation of Neurosyphilis* JAMES B. PETER, MD, PhD

365 *The Prevention of Nuclear War as a Medical Priority* HOWARD KORNFELD, MD

366 *HAFE in Nepal* E. Y. DAVIS, FRCP (Ret)

Hypophosphatemia: Correct Quantity of 50 Percent Magnesium Sulfate

366 WILLIS C. TRIPLETT, PharmD

366 JAMES P. KNOCHEL, MD, Replies

367 *Preventive Medicine in Practice: The State of the Art* DAVID J. MARON, BA
The author is a fourth-year medical student, class of 1981, University of Southern California School of Medicine, Los Angeles.

373 *Announcement of 77th Annual Meeting of Nevada State Medical Association, Carson City, May 14-17, 1981*

374 *Announcement of 95th Annual Meeting of New Mexico Medical Society, Albuquerque, May 6-8, 1981*

376 *In Memoriam*

378 *Subscription Information*

Information for Authors, See January Issue, Advertising Page 10

Practice what we teach.

Today there are over 31 million men, women and children suffering from the many forms of arthritis and related rheumatic diseases. And there just aren't enough trained rheumatologists to help them.

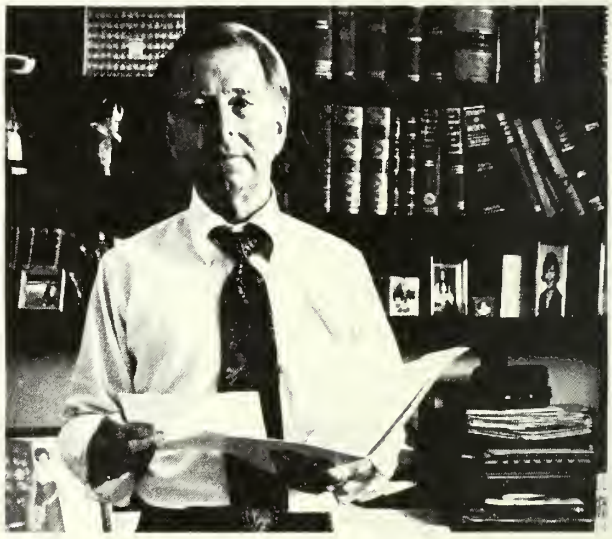
That's why arthritis sufferers need your help.

They must depend heavily on the family practitioner for better diagnosis, more effective patient treatment.

Contact your local Arthritis Foundation chapter for the latest information on arthritis. This includes continuing educational seminars by leading rheumatologists, scientific meetings, "outreach" programs—as well as the "Bulletin on the Rheumatic Diseases," "Arthritis and Rheumatism Journal," "Primer on the Rheumatic Diseases," audio cassettes and other professional materials. Free disease handbooks and medication pamphlets are also available to patients.

Please. Let us help your practice with what we teach.

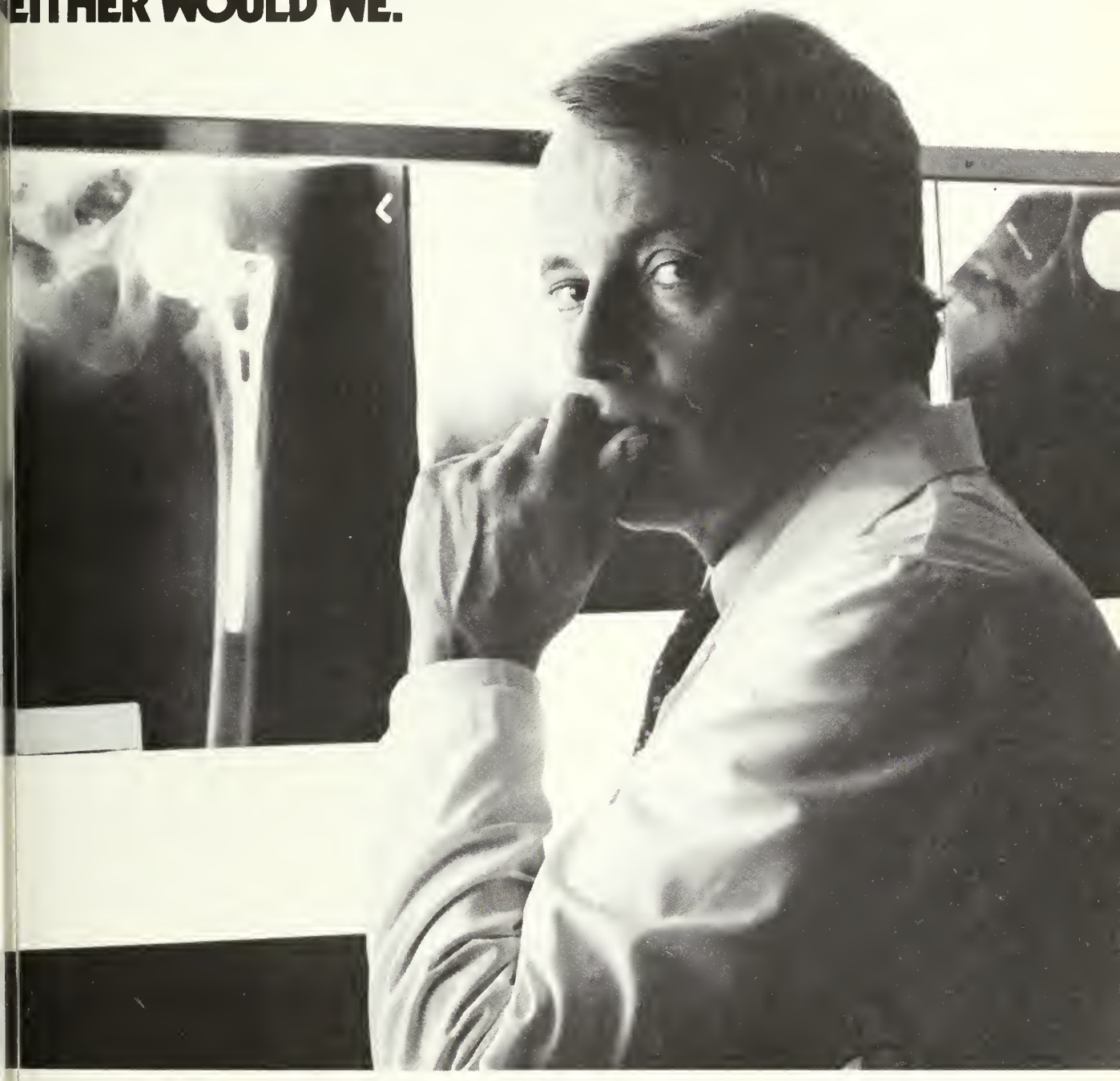
The Arthritis Foundation helps doctors help.



ARTHRITIS FOUNDATION

OULD YOU GUARANTEE THERE WON'T BE PROBLEMS VER THE NEXT 5 YEARS?

EITHER WOULD WE.



esponsible physicians know
at despite sound medical judg-
ent and specialized skills, their
rognoses are often subject to
ncertainty.

You must make allowances for
otential adversity and you should
xpect your professional liability
surance company to do the same.

Responsible medical malpractice
surers, like The Doctors' Company,
now that their policyholders' long-
ange interests are best protected
y financial strength and solvency.

That's why we maintain the largest surplus of all the doctor-owned malpractice insurers in the western United States. That's why our earned premium to surplus ratio is the most favorable of all these companies. And that's why we continue to collect surplus contributions from new members.

Future results can't be guaranteed, in the fragile art of medicine or in the volatile business of malpractice insurance. Our allowance for adversity is surplus.

For details about our program, call or write: The Doctors' Company, 233 Wilshire Blvd., Santa Monica, CA 90401. (213) 451-9936. Toll free, (800) 352-7271. Outside California, (800) 421-2368.

THE DOCTORS' COMPANY

AN INTERINSURANCE EXCHANGE
OFFERING MEDICAL MALPRACTICE INSURANCE
TO DOCTORS IN
CALIFORNIA, NEVADA, WYOMING AND MONTANA

This program is approved for 10 credit hours Category 1 for the AMA and CMA certification program

BMA in USA

BRITISH MEDICAL ASSOCIATION CONGRESS, SAN DIEGO

19-22 OCTOBER 1981

The British Medical Association's international clinical meetings are accepted as notable dates in the medical calendar. From 19-22 October this year, hundreds of doctors from Britain and the USA will meet in San Diego's Town and Country Hotel for the BMA's Congress, held in co-operation with the California Medical Association and the San Diego County Medical Society.

The Congress will be opened by the well-known historian and broadcaster, Mr. Alistair Cooke, and many leading surgeons and physicians from Britain and America will be taking part. The names of the other main speakers will be announced later. There is an extensive social program for the families of doctors attending.

PROGRAM

Monday 19 October

10.30	Introductory talk by Mrs. Pat Houston, San Diego Convention Bureau
12.00	International Health Care Exhibition opens
19.30	Opening ceremony and keynote address by Mr. Alistair Cooke
20.30	Welcome reception

Tuesday 20 October

08.30-10.45	Plenary session I: "Doctors in jeopardy" 1. Malpractice 2. The sick doctor
11.15-12.30	Simultaneous sessions: 1. Medical audit or quality control 2. Legal threats to medicine 3. Research constraints Medical films
Afternoon	Medical visits, exhibition seminars
19.00	Private hospitality

Wednesday 21 October

08.30-10.15	Plenary session II: 'The management of breast cancer"

Wednesday 21 October *continued*

10.45-12.30	Simultaneous sessions: 1. Terminal care and the hospice 2. Women in medicine 3. Geriatric medicine Medical films
14.30-16.00	Simultaneous sessions: 1. The National Health Service 2. The physician and the stress on his family 3. Who runs the hospitals? Medical visits
17.00	Sea World visit and dinner

Thursday 22 October

08.30-10.15	Plenary session III: "Chronic disability —the new leprosy?"
10.45-12.30	Simultaneous sessions: 1. Screening 2. Role of the paramedic 3. The day case—anaesthesia, surgery and other problems Medical films
Afternoon	Exhibition seminars
19.30	Farewell Banquet

Registration

The congress fees are as follows:

Any doctor from the USA, Central or South America **US$ 75**

All other countries including Canada **US$115**

(In the case of British doctors, only BMA members will be eligible to attend)

Late registration fee after 31 July 1981 US$140

No registration fee will be charged for accompanying persons. The congress fee includes morning coffee and attendance at any of the scientific sessions at the Town and Country Hotel, two tickets for the keynote address and welcome reception on 19 October, transport to medical visits, and one ticket for a morning tour for accompanying persons.

Exhibition

An international health care exhibition will be held at the Town and Country Hotel and Convention Center in San Diego during the Congress.

Where to apply

Doctors from the USA, Canada or Central or South America should apply to Mr. G. Denney, associate executive director, San Diego Medical Society, 3702 Ruffin Road, San Diego, California 92123. Telephone: (714) 565 8888.

CONTINUING MEDICAL EDUCATION

California, Hawaii, Nevada; Alaska, Montana, Idaho; New Mexico; Oregon; Washington; Utah

CALIFORNIA, HAWAII and NEVADA

This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000, ext. 146. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

May 3-9—**17th Biennial Western Conference on Anesthesiology.** Hawaiian Regent Hotel, Waikiki (3-7) and Intercontinental Hotel, Maui (8-9). One week. 26 hrs. Contact: Biennial Western Conf. on Anesthesiology, Group Travel Unlimited, 700 Larkspur Landing Circle, Suite 169, Larkspur 94939.

June 4-7—**California Society of Anesthesiologists—Annual Scientific Meeting.** Hyatt Regency, San Francisco. Thursday-Sunday. 20 hrs. $100, members; $200, nonmembers. Contact: CSA, 100 E. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

August 23-25—**Neuro-Anesthesia.** UCSD at Village Inn, La Jolla. Sunday-Tuesday.

September 12-13—**Weekend Seminar.** Calif. Society of Anesthesiologists at Sahara Hotel, Lake Tahoe. Saturday-Sunday. Contact: CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

CANCER

April 25—**Oncology Update: 1981.** Northridge Hospital at Century Plaza Hotel, Los Angeles. Saturday. 8 hrs. $125. Contact: Sandra Rozzen, Dept. of Med. Ed., Northridge Hosp., 18300 Roscoe Blvd., Northridge 91328. (213) 885-5311.

April 25—**Breast Cancer: Current Views.** UCLA. Saturday.

May 18-22—**Medical Oncology Review.** American College of Physicians at University of Hawaii School of Medicine, Honolulu. Monday-Friday. Contact: Postgraduate Dept., ACP, 4200 Pine St., Philadelphia, PA 19104. (215) 243-1200.

June 10—**Carcinomas of the Uterus and Ovaries.** LLU. Wednesday. 4 hrs. $30.

June 13-17—**Head and Neck Oncology.** UCLA. Saturday-Wednesday.

EMERGENCY MEDICINE

April 18-25—**Emergency Medical Care.** Univ. of Washington School of Medicine at Wailea Beach, Maui. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

April 24-26—**Advanced Cardiac Life Support Workshops.** Emergency Medical Systems at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact. EMS, 2310 Mason St., San Francisco 94133. (415) 956-5900.

April 25-May 2—**Emergency Medicine.** USC at Royal Lahaina Hotel, Maui. One week. $350.

April 27-May 1—**Advanced Problems in Cardiac Emergencies.** UCSD at Kauai, Hawaii. Monday-Friday. 21 hrs. $325.

May 4-8—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $425.

May 7-9—**Cardiovascular Emergencies.** See Medicine, May 7-9.

May 7, 14, 21, 28—**Trauma.** Northridge Hospital Medical Center, Northridge. Thursdays. Contact: Dept. of Med. Ed., Northridge Hosp. Med. Ctr., 18300 Roscoe Blvd., Northridge 91328. (213) 885-5311.

May 13—**Emergency Medicine.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6 hrs. $35. Contact: Cont. Med. Ed., N. T. Enloe Mem. Hosp., 5th Ave. and The Esplanade, Chico 95926. (800) 822-8102, ext. 7375.

May 25-26—**Advanced Cardiac Life Support.** Emergency Care Education Center at Queen Mary, Long Beach. Monday-Tuesday. 12 hrs. $130. Contact: ECEC, P.O. Box 9639, Marina Del Rey 90291. (213) 822-1312.

May 26-30—**California Chapter, American College of Emergency Physicians—10th Annual Scientific Assembly.** Jack Tar Hotel, San Francisco. Tuesday-Saturday. Contact: Calif. Chap., ACEP, 6839 Lincoln Blvd., Suite 240, Los Angeles 90045.

(Continued on Page 19)

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center 2801 Atlantic Ave., Long Beach 90801. (213) 595-3837.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

When she can't manage, you can.

The sweats. The hot flushes. The distress and discomfort of atrophic vaginitis. The possibility of osteoporosis.* The menopause.

For many women, it's a time of confusion and frustration. Counseling can help her overcome these feelings. But counseling *can't* stop vasomotor and vaginal symptoms, or retard bone loss*...the true signs of estrogen deficiency. And that's where she needs you most.

You're an expert at estrogen replacement. You know why it should be used. When it's best avoided. How to cycle therapy. Determine dosage. Check for contraindications and possible complications. Follow-up. You know when therapy should begin, and when it deserves to end.

Most of all, you know your patient—and when she needs the effective relief you can give her with PREMARIN.

When it comes to managing the estrogen-deficiency symptoms of the menopause, you've got what it takes.

*Conjugated Estrogens Tablets have been evaluated as probably effective for postmenopausal osteoporosis

Prescribed with care by physicians who care.

PREMARIN®
BRAND OF
CONJUGATED ESTROGENS TABLETS, U.S.P.
0.3 mg/0.625 mg/1.25 mg/2.5 mg

Please see following page for brief summary of prescribing information.

BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION, SEE PACKAGE CIRCULAR)

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA

Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year.[1-3] This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade.[4] The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment[1] and on estrogen dose.[3] In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized, and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration.[1] It therefore appears prudent to utilize such a regimen. Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY

The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare.[5,6] This risk has been estimated as not greater than 4 per 1000 exposures.[7] Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis,[8-12] epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes. Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects.[13-16] One case control study[16] estimated a 4.7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses. If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

DESCRIPTION: PREMARIN (Conjugated Estrogens Tablets, U.S.P.) for oral administration contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters.

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications for use as follows:

Effective:

1. Moderate to severe *vasomotor* symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions.)
2. Atrophic vaginitis.
3. Kraurosis vulvae.
4. Female hypogonadism.
5. Female castration.
6. Primary ovarian failure.
7. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.
8. Prostatic carcinoma—palliative therapy of advanced disease.
9. Postpartum breast engorgement—Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy. Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens.[19]

PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND IT'S USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy and good general health-promoting measures. Final classification of this indication requires further investigation.

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions. 1. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease. 2. Known or suspected estrogen-dependent neoplasia. 3. Known or suspected pregnancy. (See Boxed Warning). 4. Undiagnosed abnormal genital bleeding. 5. Active thrombophlebitis or thromboembolic disorders. 6. A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).

WARNINGS: At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast,[17] although a recent study has raised this possibility.[18] There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms. A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens.[17]

Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement; it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement.[19-22] Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction.[23-30] Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users.[31,32] An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives.[33,34] If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization. Estrogens should not be used in persons with active thrombophlebitis, thromboembolic disorders, or in persons with a history of such disorders in association with estrogen use. They should be used with caution in patients with cerebral vascular or coronary artery disease. Large doses (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown[35] to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. When doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a clear risk.

Benign hepatic adenomas should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives.[36] Increased blood pressure may occur with use of estrogens in the menopause[37] and blood pressure should be monitored with estrogen use. A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed. Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed. Conditions influenced by fluid retention such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc. Oral contraceptives appear to be associated with an increased incidence of mental depression.[38] Patients with a history of depression should be carefully observed. Preexisting uterine leiomyomata may increase in size during estrogen use. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated. Estrogens should be used with care in patients with impaired liver function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete.

The following changes may be expected with larger doses of estrogen:

a. Increased sulfobromophthalein retention.

b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.

d. Impaired glucose tolerance.

e. Decreased pregnanediol excretion.

f. Reduced response to metyrapone test.

g. Reduced serum folate concentration.

h. Increased serum triglyceride and phospholipid concentration.

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives: breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhea, premenstrual-like syndrome, amenorrhea during and after treatment, increase in size of uterine fibromyomata, vaginal candidiasis, change in cervical erosion and in degree of cervical secretion, cystitis-like syndrome, tenderness, enlargement, secretion (of breasts), nausea, vomiting, abdominal cramps, bloating, cholestatic jaundice, chloasma or melasma which may persist when drug is discontinued, erythema multiforme, erythema nodosum, hemorrhagic eruption, loss of scalp hair, hirsutism, steepening of corneal curvature, intolerance to contact lenses, headache, migraine, dizziness, mental depression, chorea, increase or decrease in weight, reduced carbohydrate tolerance, aggravation of porphyria, edema, changes in libido.

ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION: 1. *Given cyclically for short term use only.* For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0.3 to 1.25 mg or more daily).

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (e.g. three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

2. *Given cyclically.* Female hypogonadism. Female castration. Primary ovarian failure. Osteoporosis.

Female hypogonadism—2.5 to 7.5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration. If bleeding does not occur by the end of this period, the same dosage schedule is repeated. The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium.

If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U.S.P.), 2.5 to 7.5 mg daily in divided doses, for 20 days. During the last five days of estrogen therapy, give an oral progestin. If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding.

Female castration and primary ovarian failure—1.25 mg daily cyclically. Adjust upward or downward according to response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

Osteoporosis (to retard progression)—1.25 mg daily, cyclically.

3. *Given for a few days.* Prevention of postpartum breast engorgement—3.75 mg every four hours for five doses, or 1.25 mg every four hours for five days.

4. *Given chronically.* Inoperable progressing prostatic cancer—1.25 to 2.5 mg three times daily.

Inoperable progressing breast cancer in appropriately selected men and postmenopausal women—10 mg three times daily for a period of at least three months.

Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U.S.P.) No. 865—Each *purple* tablet contains 2.5 mg in bottles of 100 and 1,000. No. 866—Each *yellow* tablet contains 1.25 mg in bottles of 100 and 1,000. Also in unit dose package of 100. No. 867—Each *red* tablet contains 0.625 mg in bottles of 100 and 1,000. Also in unit dose package of 100. No. 868—Each *green* tablet contains 0.3 mg in bottles of 100 and 1,000.

PHYSICIAN REFERENCES: 1. Ziel, H.K., *et al.*: N. Engl. J. Med. *293*:1167-1170, 1975. 2. Smith, D.C., *et al.*: N. Engl. J. Med. *293*:1164-1167, 1975. 3. Mack, T.M., *et al.*: N. Engl. J. Med. *294*:1262-1267, 1976. 4. Weiss, N.S., *et al.*: N. Engl. J. Med. *294*:1259-1262, 1976. 5. Herbst, A.L., *et al.*: N. Engl. J. Med. *284*:878-881, 1971. 6. Greenwald, P., *et al.*: N. Engl. J. Med. *285*:390-392, 1971. 7. Lanier, A., *et al.*: Mayo Clin. Proc. *48*:793-799, 1973. 8. Herbst, A., *et al.*: Obstet. Gynecol. *40*:287-298, 1972. 9. Herbst, A., *et al.*: Am. J. Obstet. Gynecol. *118*:607-615, 1974. 10. Herbst, A., *et al.*: N. Engl. J. Med. *292*:334-339, 1975. 11. Stafl, A., *et al.*: Obstet. Gynecol. *43*:118-128, 1974. 12. Sherman, A.I., *et al.*: Obstet. Gynecol. *44*:531-545, 1974. 13. Gal, I., *et al.*: Nature *216*:83, 1967. 14. Levy, E.P., *et al.*: Lancet *1*:611, 1973. 15. Nora, J., *et al.*: Lancet *1*:941-942, 1973. 16. Janerich, D.T., *et al.*: N. Engl. J. Med. *291*:697-700, 1974. 17. Boston Collaborative Drug Surveillance Program: N. Engl. J. Med. *290*:15-19, 1974. 18. Hoover, R., *et al.*: N. Engl. J. Med. *295*:401-405, 1976. 19. Daniel, D.G., *et al.*: Lancet *2*:287-289, 1967. 20. The Veterans Administration Cooperative Urological Research Group: J. Urol. *98*:516-522, 1967. 21. Bailar, J.C.: Lancet *2*:560, 1967. 22. Blackard, C., *et al.*: Cancer *26*:249-256, 1970. 23. Royal College of General Practitioners: J. R. Coll. Gen. Pract. *13*:267-279, 1967. 23a. Royal College of General Practitioners: Oral Contraceptives and Health, New York, Pitman Corp., 1974. 24. Inman, W.H.W., *et al.*: Br. Med. J. *2*:193-199, 1968. 25. Vessey, M.P., *et al.*: Br. Med. J. *2*:651-657, 1969. 26. Sartwell, P.E., *et al.*: Am. J. Epidemiol. *90*:365-380, 1969. 27. Collaborative Group for the Study of Stroke in Young Women: N. Engl. J. Med. *288*:871-878, 1973. 28. Collaborative Group for the Study of Stroke in Young Women: J.A.M.A. *231*:718-722, 1975. 29. Mann, J.I., *et al.*: Br. Med. J. *2*:245-248, 1975. 30. Mann, J.I., *et al.*: Br. Med. J. *2*:241-245, 1975. 31. Inman, W.H.W., *et al.*: Br. Med. J. *2*:203-209, 1970. 32. Stolley, P.D., *et al.*: Am. J. Epidemiol. *102*:197-208, 1975. 33. Vessey, M.P., *et al.*: Br. Med. J. *3*:123-126, 1970. 34. Greene, G.R., *et al.*: Am. J. Public Health *62*:680-685, 1972. 35. Coronary Drug Project Research Group: J.A.M.A. *214*:1303-1313, 1970. 36. Mays, E.T., *et al.*: J.A.M.A. *235*:730-732, 1976. 37. Pfeffer, R.I., *et al.*: Am. J. Epidemiol. *103*:445-456, 1976.

7457/181

Ayerst AYERST LABORATORIES
New York, N.Y. 10017

(Continued from Page 15)

May 28-30—**3rd Annual Trauma Seminar.** DREW at Disneyland Hotel, Anaheim. Thursday-Saturday. Contact: S. Balasubramaniam, MD, Div. of Emergency Medicine, Charles R. Drew Postgraduate Medical School, 1621 E. 120th St., Los Angeles 90059. (213) 603-5235.

June 15-19—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $425.

June 26-27—**Orthopedics in Emergency Medicine—An In-Depth Review.** UCLA at Miramar-Sheraton Hotel, Santa Monica. Friday-Saturday. 14 hrs. $180.

June 29-July 3—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

July 24-26—**Advanced Cardiac Life Support Workshops.** Emergency Medical Systems at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact. EMS, 2310 Mason St., San Francisco 94133. (415) 956-5900.

July 27-28—**Advanced Cardiac Life Support.** Emergency Care Education Center at Queen Mary, Long Beach. Monday-Tuesday. 12 hrs. $130. Contact: ECEC, P.O. Box 9639, Marina Del Rey 90291. (213) 822-1312.

August 3-7—**Postgraduate Institute for Emergency Room Physicians, Symposium II.** UCSD. Monday-Friday. 40 hrs. $425.

September 14-18—**Postgraduate Institute for Emergency Room Physicians, Symposium I.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $425.

September 28-29—**Advanced Cardiac Life Support.** Emergency Care Education Center at Queen Mary, Long Beach. Monday-Tuesday. 12 hrs. $130. Contact: ECEC, P.O. Box 9639, Marina Del Rey 90291. (213) 822-1312.

October 2-3—**Symposium on Medical Emergencies.** UCLA at Miramar-Sheraton Hotel, Santa Monica. Friday-Saturday. 14 hrs. $180.

October 19-23—**Postgraduate Institute for Emergency Room Physicians, Symposium III.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $425.

MEDICINE

May 1-2—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Sheraton Fisherman's Wharf, San Francisco. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

May 1-3—**Practical Dermatology for the Primary Care Physician.** UCLA at Sheraton Hotel, Santa Barbara. Friday-Sunday. 8 hrs. $190.

May 6—**Respiratory.** St. Francis Medical Center, Lynwood. Wednesday. 6 hrs. Contact: Allan M. Hoffman, EdD, Dir. of Med. Ed., St. Francis Med. Ctr., 3630 Imperial Highway, Lynwood 90262. (213) 603-6174.

May 6—**Thyroid '81.** Hospital of the Good Samaritan at Bonaventure Hotel, Los Angeles. Wednesday. 7 hrs. Contact: Mary Jane Thompson, Hosp. of the Good Samaritan, 616 S. Witmer St., Los Angeles 90017. (213) 488-8908.

May 6—**Young Investigators Forum.** American Heart Assn.-Greater Los Angeles Affiliate at UCLA. Wednesday. 6 hrs. Contact: LaVerna M. Titus, AHA-GLAA, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

May 7-9—**Cardiovascular Emergencies.** American College of Cardiology and PMC at Mark Hopkins Hotel, San Francisco. Thursday-Saturday. 18 hrs. Contact: Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

May 8-9—**Gastrointestinal Imaging in Perspective.** UCSF Extended Programs in Medical Education, Central San Joaquin Valley Branch, at Piccadilly Inn, Fresno. Friday-Saturday. Contact: Kathleen Wolff, 5110 E. Clinton, Suite 201, Fresno 93727. (209) 252-1948.

May 8-10—**Cardiac Ischemia and Arrhythmias—Current Concepts for Diagnosis and Treatment.** International Medical Education Corp. at Sahara Hotel, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

May 14-15—**Diagnosis and Therapy of Cardiovascular Disease.** American Heart Assn., Calif. Affiliate, at Monterey Conference Center, Monterey. Thursday-Friday. 11 hrs. $70. Contact: A. M. Austin, RN, 805 Burlway Rd., Burlingame 94101. (415) 342-5522.

May 18-21—**Endocrinology for the Practicing Physician.** LLU at Mauna Kea Beach Hotel, Kamuela, Hawaii. Monday-Thursday. 16 hrs. $200.

May 18-22—**Advances in Internal Medicine.** UCSF at Hyatt on Union Square, San Francisco. Monday-Friday.

May 23-30—**Allergy and Immunology.** Univ. of Washington School of Medicine at Wailea Beach, Maui, Hawaii. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle 98195.

May 31-June 4—**Internal Medicine for the Generalist—1981.** UCSD at Hilton, San Diego. Sunday-Thursday. 23 hrs.

June 1-5—**Advances in Internal Medicine.** UCSF. Monday-Friday.

June 3—**Gastroenterology.** St. Francis Medical Center, Lynwood. Wednesday. 6 hrs. Contact: Allan M. Hoffman, EdD, Dir. of Med. Ed., St. Francis Med. Ctr., 3630 Imperial Highway, Lynwood 90262. (213) 603-6174.

June 12-14—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Sahara Hotel, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

June 26-28—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Sheraton, Anaheim. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

July 13-17—**Third International Psoriasis Symposium.** STAN. Monday-Friday.

July 18-25—**Cardiovascular Medicine and Surgery: An Advanced Course.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 23 hrs. $295.

August 7-8—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Doubletree Inn, Monterey. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

August 12-15—**Workshop in Medical Mycology/Dermatomycology.** Memorial Hospital Medical Center-UCI Center for Health Education at Newporter Inn, Newport Beach. Wednesday-Saturday. Contact: Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

August 15-21—**Neuropsychiatric Issues in the Law, Education and Medicine: Hyperactivity and Dyscontrol Syndrome.** See Psychiatry, August 15-21.

August 21-22—**Cardiac Rehabilitation.** International Medical Education Corp. at Sheraton, Anaheim. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

September 5-11—**Dermatology.** UCD at Silverado Country Club, Napa. One week.

September 18-20—**Cardiac Ischemia and Arrhythmias—Current Concepts for Diagnosis and Treatment.** International Medical Education Corp. at Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

(Continued on Page 49)

The predictability of an IV infusion

Until Theo-Dur there was only one method for obtaining virtually ideal therapeutic theophylline serum levels—IV infusion.

Theo-Dur provides the therapeutic benefits of IV infusion in a tablet:

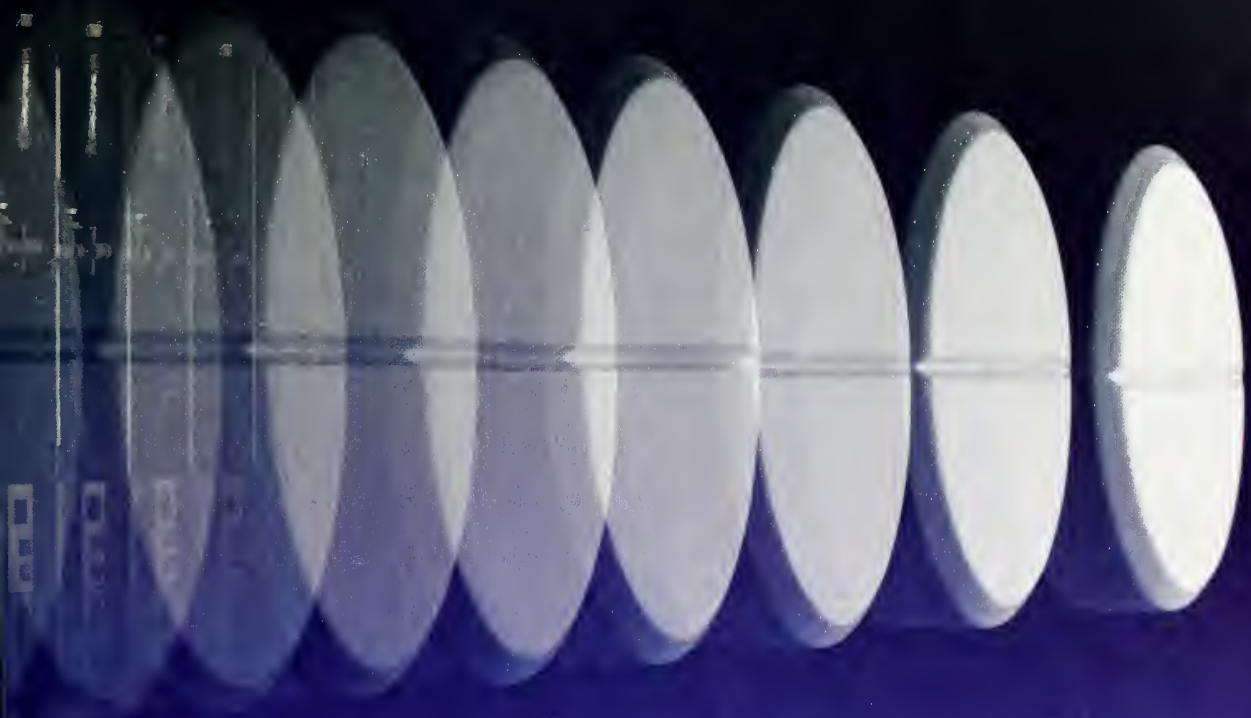
- a constant rate of theophylline absorption
- linear serum concentrations within the *therapeutic window*
- q12h dosage

© 1979 Key Pharmaceuticals, Inc.

.in a tablet

Zero-Order
THEO-DUR™
(Anhydrous Theophylline)

The only formulation with q12h dosing and zero-order absorption



ZERO-ORDER dc/dt=K™
(constant rate absorption by GI infusion)

...assures programmed availability of a theophylline dose, hour by hour, for each individual, regardless of clearance rate. Thus, Theo-Dur dosage can be individualized to provide optimal results for each patient.

Theo-Dur "locks in" on the therapeutic window. Theophylline serum concentrations between 10 and 20 mcg/ml provide the *therapeutic window* within which Theo-Dur consistently provides optimal therapeutic effect for a full 12-hour interval. Blood levels above 20 mcg/ml may cause toxicity...blood levels below 10 mcg/ml may be ineffective.

Three strengths for flexible dosage. Dosage can be easily titrated for maximum therapeutic effect. Scored tablets in 100 mg, 200 mg and 300 mg strengths permit accurate dosage adjustment in as little as 50 mg increments. Patients presently on theophylline can be easily converted to Theo-Dur by dividing the daily anhydrous theophylline intake into two equal doses administered at 12-hour intervals.

Dosage and Administration: Average initial dose is 100 mg to 300 mg q12h depending on the age and weight of the patient and the severity of the disease. See package insert for full prescribing information.

See following page for a brief summary of prescribing information.

KEY PHARMACEUTICALS, INC.
Miami, Florida 33169 (USA)

THEO-DUR™

Enduring Action Anhydrous Theophylline

Sustained Action Tablets

Description: THEO-DUR Sustained Action Tablets contain anhydrous theophylline, with no color additives.

Actions: The pharmacologic actions of theophylline are as a bronchodilator, pulmonary vasodilator and smooth muscle relaxant since the drug directly relaxes the smooth muscle of the bronchial airways and pulmonary blood vessels. Theophylline also possesses other actions typical of the xanthine derivatives: coronary vasodilator, diuretic, cardiac stimulant, cerebral stimulant and skeletal muscle stimulant. The actions of theophylline may be mediated through inhibition of phosphodiesterase and a resultant increase in intracellular cyclic AMP which could mediate smooth muscle relaxation.

Indications: Symptomatic relief and/or prevention of asthma and reversible bronchospasm associated with chronic bronchitis and emphysema

Contraindications: THEO-DUR is contraindicated in individuals who have shown hypersensitivity to any of its components or xanthine derivatives.

Warnings: Excessive theophylline doses may be associated with toxicity; serum theophylline levels should be monitored to assure maximum benefit with minimum risk. Incidence of toxicity increases at serum levels greater than 20 mcg/ml. High blood levels of theophylline resulting from conventional doses are correlated with clinical manifestations of toxicity in: patients with lowered body plasma clearances, patients with liver dysfunction or chronic obstructive lung disease, and patients who are older than 55 years of age, particularly males. There are often no early signs of less serious theophylline toxicity such as nausea and restlessness, which may appear in up to 50% of patients prior to onset of convulsions. Ventricular arrhythmias or seizures may be the first signs of toxicity.

Many patients who have higher theophylline serum levels exhibit a tachycardia. Theophylline products may worsen pre-existing arrhythmias.

Usage in Pregnancy: Safe use in pregnancy has not been established relative to possible adverse effects on fetal development, but neither have adverse effects on fetal development been established. This is, unfortunately, true for most anti-asthmatic medications. Therefore, use of theophylline in pregnant women should be balanced against the risk of uncontrolled asthma.

Precautions: THEO-DUR TABLETS SHOULD NOT BE CHEWED OR CRUSHED. Theophyllines should not be administered concurrently with other xanthine medications. It should be used with caution in patients with severe cardiac disease, severe hypoxemia, hypertension, hyperthyroidism, acute myocardial injury, cor pulmonale, congestive heart failure, liver disease and in the elderly, particularly males, and in neonates. Great caution should be used in giving theophylline to patients in congestive heart failure since these patients show markedly prolonged theophylline blood level curves. Use theophylline cautiously in patients with history of peptic ulcer. Theophylline may occasionally act as a local irritant to G.I. tract although gastrointestinal symptoms are more commonly central and associated with high serum concentrations above 20 mcg/ml.

Adverse Reactions: The most consistent adverse reactions are usually due to overdose and are:

Gastrointestinal: Nausea, vomiting, epigastric pain, hematemesis, diarrhea.

Central Nervous System: Headaches, irritability, restlessness, insomnia, reflex hyperexcitability, muscle twitching, clonic and tonic generalized convulsions.

Cardiovascular: Palpitation, tachycardia, extrasystoles, flushing, hypotension, circulatory failure, life threatening ventricular arrhythmias.

Respiratory: Tachypnea

Renal: Albuminuria, increased excretion of renal tubular cells and red blood cells; potentiation of diuresis.

Others: Hyperglycemia and inappropriate ADH syndrome.

How Supplied: THEO-DUR 100 mg, 200 mg and 300 mg Sustained Action Tablets are available in bottles of 100, 1000, and 5000, and in unit dose packages of 100 (20 x 5's).

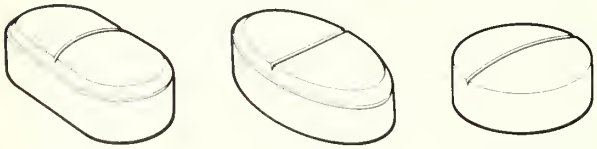
Caution: FEDERAL LAW PROHIBITS DISPENSING WITHOUT A PRESCRIPTION

For full prescribing information, see package insert. 0779

ZERO-ORDER

dc/dt=K™

(Constant rate absorption by GI infusion)



300 mg 200 mg 100 mg

KEY PHARMACEUTICALS, INC.
Miami, Florida 33169 (USA)

DOCTORS' SPECIAL!

Give your family a

Condo Vacation in Hawaii

and we'll give you use of a

Car FREE!

When you stay in a 1-bedroom oceanview or 2-bedroom condominium in one of these luxurious resorts, you'll have the use of a car free. All condominiums are on or near the beach and have daily maid service.

WAIKIKI **Island Colony or Waikiki Sunset** Pool, golf nearby and many luxury extras. From $59/day-$370/week 1-4 persons	MAUI **Kaanapali Shores** Free tennis, pool, golf nearby. From $78/day-$490/week 1-4 persons
HAWAII **Kona Lagoon** Free tennis, golf nearby. From $85/day-$535/week 1-4 persons	KAUAI **Pono Kai** Mile-long beach, free tennis, barbecue area, sauna. From $58/day-$365/week 1-4 persons

Serving Hawaii Visitors for More Than 30 Years

hcp HCP Condo Resorts

Andre S. Tatibouet, President
2299 Kuhio Avenue, Honolulu, Hawaii 96815

For reservations, beautiful four-color brochures or information about any of HCP's 18 hotels and condominiums in Hawaii, see your travel agent or call Hawaii Toll Free 800-367-5124.

Call Hawaii Toll Free 800-367-5124

Classified Advertisements

The rate for each insertion is **4.00 per line** (average six words per line) **with five line minimum.**

Box number charge: $2.00 each month.

Classified display rates $40.00 per inch.

Copy for classified advertisements should be received not later than **the fifth of the month preceding issue. All copy must be typed or printed.** • Classified advertisers using Box Numbers forbid the disclosure of their Identity. Your inquiries in writing will be forwarded to Box Number advertisers. The right is reserved to reject or modify all classified advertising copy in conformity with the rules of the Advertising Committee.

Please Type or Print Advertising Copy

CLASSIFIED ADVERTISEMENTS ARE PAYABLE IN ADVANCE

PHYSICIANS WANTED

EMERGENCY MEDICINE OPPORTUNITIES, full and part-time, in the Rocky Mountain states for career oriented emergency physicians. Excellent compensation and paid professional liability insurance. Send credentials to Mr. William Salmo, Chase Stone Center, Holly Sugar Building, Suite 440, Colorado Springs, CO 80903. Or call toll-free 1 (800) 525-3681 (in Colorado call collect (303) 471-4981).

ANESTHESIA—FRESNO, CALIFORNIA. The Valley Medical Center of Fresno, in affiliation with the UCSF School of Medicine, seeks two anesthesiologists for its Department of Anesthesia. The Valley Medical Center, a 400-bed county facility, is the principal teaching hospital of the Medical School's new clinical branch in Fresno. The positions offer excellent opportunities in clinical anesthesia, teaching and research; competitive salary. Board Certification or eligibility and California license required. Please send inquiries to: Frank L. Davidson, MD, Chief of Anesthesiology, Valley Medical Center, 445 S. Cedar Avenue, Fresno, CA 93702, (209) 453-4496.

ORTHOPEDIC SURGERY
OB/GYN
OTOLARYNGOLOGY
GENERAL SURGERY

We have immediate need of physicians in these and other disciplines to join us at INA/Ross-Loos Healthplan, now marking a half-century of service to Southern California members.

INA/Ross-Loos health centers are located throughout the region providing comprehensive care through utilization of community hospitals.

We offer the board eligible/certified physician an opportunity to grow with us in an environment of challenge, freedom from malpractice premiums, minimized paperwork and excellent fringe benefits.

Our compensation is highly competitive. Request details by phone or letter to:

ROSS LOOS MEDICAL GROUP, INC

ALLAN S. MIRKEN, MD
Director of Medical Personnel
INA/Ross-Loos Medical Center
1711 West Temple Street
Los Angeles, CA 90026
(213) 413-1313

PHYSICIANS WANTED

CALIFORNIA—B.E./B.C. Family Physician, Emergency Physician or Internist wanted for new multi-Specialty group in desirable Roseville suburb of Sacramento. Combines office practice with part-time Minor Emergency Clinic practice. Competitive salary. Fringe; leads to partnership. Excellent hospital and office facilities. One position avail. immed., one avail. in Spring, 1981. Contact: Joseph Rosenfield, Adm., Western Medical Group, 6330 Main Ave., Orangevale, CA 95662, (916) 988-9544.

COLORADO EMERGENCY MEDICINE: Directorship and Clinical positions available in Northeastern portion of the state in moderate volume emergency department. Hourly quarantee plus compensation for Director's added responsibilities. Paid professional liability insurance and other amenities. For further information contact William Salmo toll-free 1 (800) 525-3681 (within Colorado call collect (303) 471-4981); or send credentials in confidence to Chase Stone Center, Holly Sugar Building, Suite 1070, Colorado Springs, CO 80903.

WYOMING: Emergency Medicine—Summer locum tenens for experienced emergency physicians in busy resort hospital located in Jackson, Wyoming. Average of 56 hours per week with flexible scheduling arrangement. Must be available June 5 through September 14 inclusive, without exception. Excellent hourly compensation plus paid professional liability insurance. For further information, contact William Salmo at 1-(800)-525-3681 (in Colorado call collect (303) 471-4981).

GENERAL/FAMILY PRACTICE PHYSICIANS (2) needed by 31 member multi-specialty group. Excellent practice opportunity; benefits and retirement program; all practice costs paid; early shareholder status. Reply D. R. Molesworth, Administrator, San Luis Medical Clinic, Ltd., 1235 Osos Street, San Luis Obispo, CA 93401.

INTERNIST/GI to join a 13-physician, multi-specialty group in Mount Vernon, Washington. The Medical Center is located across the street from a 126-bed hospital. Stockholder status is possible after one year. Guaranteed first year salary plus liberal fringe benefits. Position available June, 1981. Contact Shane Spray, Administrator, Skagit Valley Medical Center, 1400 Kincaid, Mount Vernon, WA 98273. (206) 428-2524.

EMERGENCY DEPARTMENT OPENING—Permanent and Part-Time in our group. First year salary of $78,000 includes profit sharing and pension plan, educational allowance health insurance, and part time paid at $50 per hour. Malpractice paid. Full time averages less than 40 hours per week. ED sees 43,000 annually in a 300 bed acute care hospital located in Fresno, CA. Near the High Sierras and other recreational areas. Contact Larry Marks, MD, 546 W. Morris, Fresno, CA 93704, or call collect (209) 431-3645.

GROW WITH US IN SUNNY ARIZONA—The INA Healthplan needs physicians in family practice and most specialties in Tucson and Phoenix. Attractive salaries and comprehensive benefits including a professional development program, retirement plan, and group incentive bonus are provided. If team interaction and casual living appeal to you, send your CV to: Professional Relations, INA Healthplan, Inc., 6115 North 7th Street, Phoenix, AZ 85014.

FAMILY PRACTITIONER—Position available in a growing and dynamic pre-paid health care plan in Spokane, Washington. This is an unusual opportunity to practice comprehensive family medicine with other well trained family practitioners without many of the distractions of office management. Continuity of care, patient education/preventative medicine, and high quality personal-style care are emphasized. Excellent salary and benefits. Ample cultural, educational, and recreational resources in our city and the surrounding countryside. Address inquiry and/or CV to James Shaw, MD, INA Healthplan of Washington, North 3919 Maple Street, Spokane, WA 99205.

MEDICAL-SURGICAL CENTER

Located on the coast of Washington state we have constructed a new clinic adjacent to a 150-bed hospital serving over 70,000 people. Opportunities available include:

- Internal Medicine
- Cardiologist
- Urologists
- ENT Specialists

For further information submit C.V. to: **J. Washam, 1006 South H Street, Aberdeen, WA 98520 or call (206) 533-0450.**

ST. JOSEPH HOSPITAL

PHYSICIANS WANTED

WANTED: PEDIATRICIAN/OB/GYN/GENERAL INTERNIST—Board certified or eligible—To associate with expanding 8-man group of Multi-speciality Physicians in Tacoma, Washington—Salary $40,000 per annum with partnership after first year. Send curriculum vitae or inquiries to: Clinton F. Merrill, MD, Puget Sound Clinic, 3611 South "D" Street, Tacoma, WA 98408. Or phone collect: (206) 756-8591 or (206) 589-9499 (after hours).

CARDIOLOGIST, PULMONOLOGIST, UROLOGIST, DERMATOLOGIST, & ORTHOPEDIC HAND SURGEON: Immediate openings for fully trained, Board Certified or eligible physicians in a multi-specialty group. Complete pulmonary laboratory facilities. Attractive San Francisco Bay Area. Send CV to Recruitment Committee, San Jose Medical Clinic, 45 South 17th Street, San Jose, CA 95112.

ORTHOPEDIC SURGEON—Board Certified, Orthopedic Surgeon needed at VA Medical Center, Livermore, CA. Ideal living, good climate and clean air. Malpractice insurance not needed. Position available at present. Salary dependent upon experience and qualifications. Contact: John F. Kane, MD, Chief of Staff, VA Medical Center, Livermore, CA 94550. Tel: (415) 447-2560, ext. 204.

(Continued on Page 27)

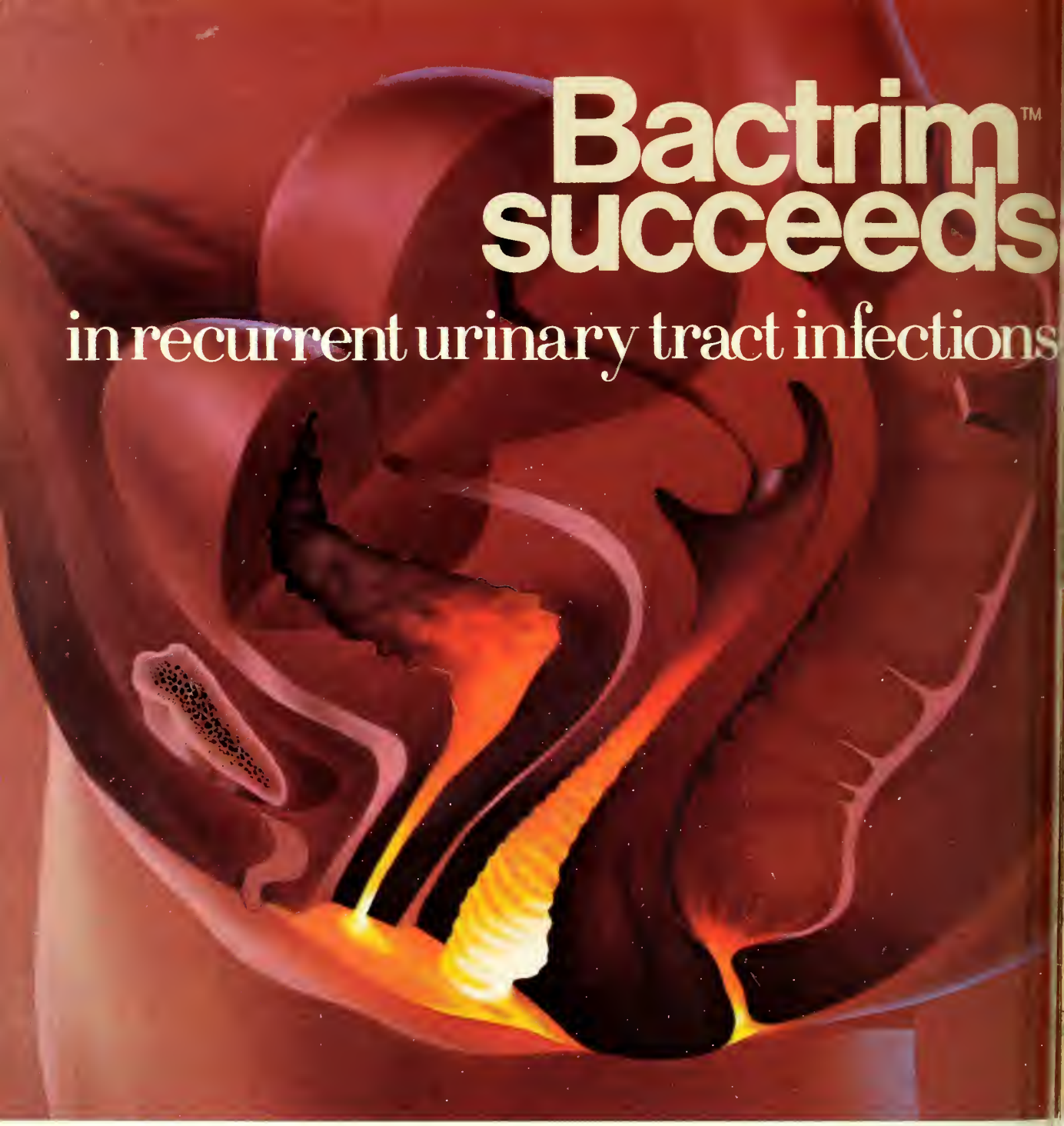
DISTRICT HEALTH OFFICER

Responsible for the administration and operation of the Spokane County Health District. Performs such actions as are necessary to organize and deliver health support services, personal and environmental health programs.

MINIMUM QUALIFICATIONS: Physician licensed to practice medicine and surgery or osteopathy and surgery in the State of Washington and who holds a degree of master in public health or its equivalent. Physicians employed as local health officers or who possess other public health related experience may be determined qualified by the State Director of Health.

SALARY: Negotiable.

APPLICANTS SHOULD SUBMIT RESUME DETAILING THEIR TRAINING AND EXPERIENCE TO SPOKANE COUNTY PERSONNEL DEPARTMENT, WEST 1116 BROADWAY, SPOKANE, WA 99260. (509) 456-5750. EOE



Bactrim™ succeeds

in recurrent urinary tract infections

from site to source

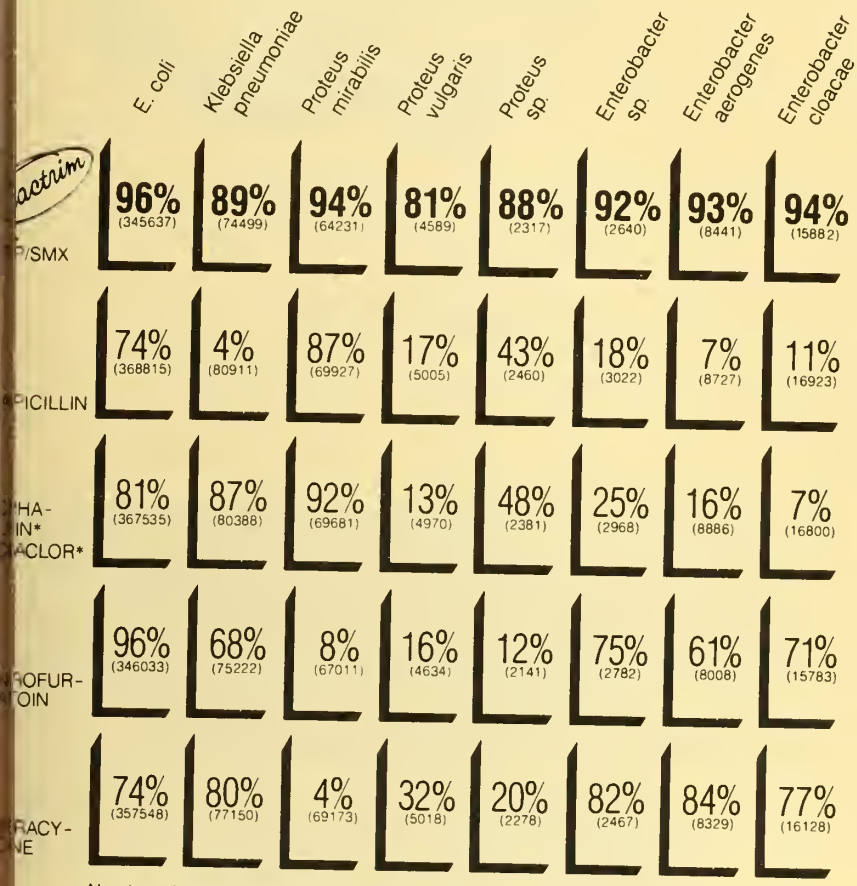
Bactrim reaches effective levels in urine, serum and renal tissue,[1] to combat infection throughout the urinary tract. The trimethoprim component enters vaginal secretions in therapeutic concentrations,[1] to prevent colonization of bacteria in the periurethral area, probably the major etiologic factor in recurrent UTI.[2,3] And in the fecal flora, Bactrim eradicates Enterobacteriaceae with no resulting emergence of resistant organisms and without adverse effect on the normal intestinal flora.

*due to susceptible *E. coli, Klebsiella-Enterobacter, Proteus mirabilis, P. vulgaris* and *P. morga*

Data from 231 hospitals, compiled by an independent bacteriologic monitoring service, show:

More isolates of more common uropathogens sensitive to Bactrim than to any other frequently prescribed antimicrobial

Per cent of isolates of common uropathogens sensitive to Bactrim and to other antimicrobials



Numbers in parentheses indicate projected number of isolates tested with antibacterial.
Source: BacData Medical Information Systems, Inc , Summer 1980.
*Tested with cephalothin disc, recommended as representative of all cephalosporins

Bactrim consistently proves its *in vitro* effectiveness against the organisms estimated to cause 90-95% of urinary tract infections: *E. coli, Proteus mirabilis, Klebsiella* and *Enterobacter* species.[4,5] Susceptibility tests are believed to correlate more closely with clinical results in urinary tract infections than in any other kind.[4]

No significant change seen in resistance patterns

Uropathogens sensitive to Bactrim have demonstrated no significant increased resistance *in vitro* after many years of use in patients with urinary tract infection.[6] In one study,[7] SMX/TMP (Bactrim), given over a period of four weeks, was not followed by emergence of resistant strains of Enterobacteriaceae—a result noted to correlate with clinical findings that in patients given SMX/TMP, urinary tract reinfections with resistant organisms are rare.

It is important to maintain adequate fluid intake during therapy. Bactrim is contraindicated during pregnancy at term, the nursing period, in patients hypersensitive to its components, and in infants under 2 months of age.

References: **1.** Rubin RH, Swartz MN: *N Engl J Med 303*: 426-432, Aug 21, 1980. **2.** Dhalla S, Flynn JT: *NY State J Med 80* 1087-1094, June 1980 **3.** Stamey TA *J Urol 109* 467-472, Mar 1973 **4.** Kunin CM. *Detection, Prevention and Management of Urinary Tract Infections*, ed 3. Philadelphia, Lea & Febiger, 1979, pp. 91, 140. **5.** Mayer TR: *Geriatrics* 35: 67-77, Mar 1980. **6.** BacData Medical Information Systems, Inc., Winter 1976-1977 to Summer 1980. **7.** Knothe H. *Infection 7* (Suppl 4): S321-S323, 1979

Bactrim™ DS

160 mg trimethoprim and 800 mg sulfamethoxazole

maximizes results with B.I.D. convenience

ROCHE®

Please see summary of product information on following page.

Bactrim™ DS

160 mg trimethoprim and 800 mg sulfamethoxazole

Before prescribing, pleeee consult compiste product informetion, e eummery of which follows:

Indicetions end Ussge: For the treetment of urinary trect infections dus to susceptible streins of the following orgenisms: *Escherichia coli, Klebsisiie-Enterobacter, Proteus mirebiis, Proteus vulgeris, Proteus morganii.* It is recommsnded thet initiel spisodse of uncomplicsted urinery trect infectione be trseted with e single effective sntibecteriel egent rether then ths combinetion. *Note:* The increasing frequency of resistant organisms limits the usefulness of all antibacterials, especially in these urinary tract infections.

For acute otitis medie in childrsn dus to susceptible strsins of *Heemophilus influenzes* or *Streptococcus pneumonies* when in physicisn's judgment it offers en edventegs over other entimicrobiels. Limitsd clinicsl informstion preeently eveilebie on effectiveness of trestmsnt of otitis medie with Bectrim whsn infection is due to empicillin-reeletsnt *Hssmophilus influenzee*. To dete, thsrs srs limitsd dsts on the ssfsty of repestsd uss of Bsctrim in children undsr two yeers of sgs. Bectrim is not indiceted for prophylsctic or prolongsd edminietrstion in otitis msdis st sny egs.

For ecute execerbetione of chronic bronchitis in edults dus to suscsptibls strsins of *Heemophilus influsnzee* or *Streptococcus pneumoniee* when in phyeicien's judgment it offers sn sdventegs over e eingle sntimicrobisl egent.

For entsritis due to eueceptible strsins of *Shigells flexneri* end *Shigelle sonnei* when entibsctsrisl therepy ie indiceted.

Also for the treetment of documented *Pneumocystis csrinii* pneumonitie. To dete, this drug hes besn tssted only in pstisnts 9 months to 16 yssrs of sgs who wsre immunosuppresssd by csncsr thsrepy.

Contreindicetions: Hypersensitivity to trimethoprim or sulfonamides; patients with documented megaloblastic anemia due to folate deficiency; pregnancy at term; nursing mothers because sulfonamides are excreted in human milk and may cause kernicterus; infants less than 2 months of age.

Wernings: BACTRIM SHOULD NOT BE USED TO TREAT STREPTOCOCCAL PHARYNGITIS. Clinical studies show that patients with group A β-hemolytic streptococcal tonsillopharyngitis have higher incidence of bacteriologic failure when treated with Bactrim than do those treated with penicillin. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides. Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended; therapy should be discontinued if a significantly reduced count of any formed blood element is noted.

Precsutions: *General.* Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In patients with glucose-6-phosphate dehydrogenase deficiency, hemolysis, frequently dose-related, may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function. Bactrim may prolong prothrombin time in those receiving warfarin; reassess coagulation time when administering Bactrim to these patients. *Pregnancy.* Teratogenic Effects. Pregnancy Category C. Because trimethoprim and sulfamethoxazole may interfere with folic acid metabolism, use during pregnancy only if potential benefits justify the potential risk to the fetus.

Adverse Rsectione: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. *Blood dyscrasias.* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic reactions.* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal reactions.* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. *CNS reactions.* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous reactions.* Drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia in patients; cross-sensitivity with these agents may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.

Dossge: Not recommsnded for infente leee then two months of sgs.

URINARY TRACT INFECTIONS AND SHIGELLOSIS IN ADULTS AND CHILDREN, AND ACUTE OTITIS MEDIA IN CHILDREN

Adults. Usual adult dosage for urinary tract infections—1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 10-14 days. Use identical daily dosage for 5 days for shigellosis.

Children: Recommended dosage for children with urinary tract infections or acute otitis media—8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, in two divided doses for 10 days. Use identical daily dosage for 5 days for shigellosis.

For patients with renal impairment. Use recommended dosage regimen when creatinine clearance is above 30 ml/min. If creatinine clearance is between 15 and 30 ml/min, use one-half the usual regimen. Bactrim is not recommended if creatinine clearance is below 15 ml/min.

ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS IN ADULTS

Usual adult dosage. 1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 14 days.

PNEUMOCYSTIS CARINII PNEUMONITIS

Recommended dosage: 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours in equal doses every 6 hours for 14 days. See complete product information for suggested children's dosage table.

Supplisd: *Double Strength (DS) tablets*, each containing 160 mg trimethoprim and 800 mg sulfamethoxazole, bottles of 100, Tel-E-Dose® packages of 100, Prescription Paks of 20 and 28. *Tablets*, each containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 100 and 500, Tel-E-Dose® packages of 100, Prescription Paks of 40. *Pediatric Suspension*, containing 40 mg trimethoprim and 200 mg sulfamethoxazole per teaspoonful (5 ml), cherry flavored—bottles of 100 ml and 16 oz (1 pint). *Suspension*, containing 40 mg trimethoprim and 200 mg sulfamethoxazole per teaspoonful (5 ml), fruit-licorice flavored—bottles of 16 oz (1 pint).

ROCHE

ROCHE LABORATORIES
Division of Hoffmann-La Roche Inc
Nutley, New Jersey 07110

Two convenient dosage forms: 100 mg (white) and 300 mg (peach) Scored Tablets

Tablets imprinted with brand name to assist in tablet identification.

Wellcome

Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

SPECIAL OFF-SEASON RATES

Maui Eldorado... The Best of Kaanapali!

A luxury lowrise resort fronted by the Royal Kaanapali Golf Course — and Kaanapali Beach! Enjoy golf, tennis, swimming in 3 pools, private beach cabana. Studios and 1 & 2 bedroom apartments. Restaurant.

Maui Eldorado RESORT

SPECIAL REDUCED OFF-SEASON RATES
Effective April 1-Dec. 15, 1981

	Ocean/Golf View	Pool/Garden View
RATES:	**Nitely**	**Nitely**
Studio (1–2 pers.)	$ 56	$ 49
1 Bdrm (1–4 pers.)	$ 69	$ 79
2 Bdrm (1–6 pers.)	$139	$119

For Reservations: Write or phone Maui Eldorado, Kaanapali, Maui, Hi 96761. Phone (606) 661-0021. **Phone Toll Free** in Continental U.S. (600) 421-0660 — In Calif. (600) 252-0076. **Or See Your Travel Agent.**

(Continued from Page 23)

PHYSICIANS WANTED

SAN FRANCISCO. GP, FP, or Internist to join 3 man FG group, must be interested to become partner after 1 year. Adjacent St. Luke's Hospital. For further details call or write, L. D. Duffield, MD, 3620 Army St., San Francisco, CA 94110. Tel: (415) 826-7575.

LAS VEGAS, NEVADA: Emergency Medicine Opportunity-Clinical position available in this modern facility south of Las Vegas. Flexible scheduling according to individual needs allows time to enjoy the numerous recreational facilities in the surrounding countryside. Minimum guarantee plus paid professional liability insurance. For details send credentials in confidence to William Salmo, Chase Stone Center, Holly Sugar Building, Suite 1070, Colorado Springs, CO 80903 or call toll-free 1 (800) 525-3681 (within Colorado, call collect (303) 471-4981).

WESTERN ARIZONA AND SOUTHERN NEVADA —EMERGENCY MEDICINE: Clinical and Directorship positions available in several emergency departments. Excellent compensation, paid professional liability insurance, flexible scheduling. For further details contact William Salmo toll-free at 1 (800) 525-3681 (within Colorado call collect (303) 471-4981); or send credentials in complete confidence to Chase Stone Center, Holly Sugar Building, Suite 1070, Colorado Springs, CO 80903.

PEDIATRICIAN WANTED FOR MONTEREY COUNTY to join well established (3) board certified pediatricians in private practice serving community of 100,000, starting summer of 1981. Attn: D. R. King, MD, 505 E. Romie Lane, Salinas, CA 93901.

PHYSICIANS WANTED

FRESNO-BAKERSFIELD-OXNARD. Family Medical Center, a primary care group practice, has positions available for Bd. Cert./Elig. Gen. Pract. or Internist. Minimum guarantee, partnerships available. New facilities, all administrative services provided. Contact: S. Lee, P.O. Box 8013, Fresno, CA 93747. (209) 252-1618.

CHIEF OF PEDIATRICS—FRESNO, CALIFORNIA. The Valley Medical Center of Fresno, in affiliation with the University of California San Francisco School of Medicine is searching for a Chief of its Pediatric Service and director of the Pediatrics residency program and associated medical student clerkships. Valley Medical Center, a 400-bed county facility, is the principal teaching hospital of the UCSF Medical School's new clinical branch in the Fresno-central San Joaquin Valley region of California. The training program in pediatrics (18 residents) which places emphasis on primary care is integrated with the Valley Children's Hospital of Fresno. We seek an individual with significant background of experience in clinical teaching, research and academic administration in pediatrics who would qualify for appointment at Associate Professor or Professor level. Please direct inquiries to the chairman of the search committee: Roger Larson, MD, Assistant Dean/Director of Medical Affairs, Valley Medical Center, 445 S. Cedar Avenue, Fresno, CA 93702, (209) 453-4390.

STUDENT HEALTH PHYSICIAN—San Jose State University 12 hours per week/10 month position, $1,316/month. Specializing in orthopedic medicine. Must be Board certified orthopedist by California Board of Medical Quality Assurance. Send résumé to R. C. Miller, MD, Director, Student Health Service, San Jose State University, San Jose, CA 95192.

PHYSICIANS WANTED

GENERAL SURGEON: Bd elg./cert. needed by 8-man multispecialty Group in King City, Monterey County, California, "Steinbeck Country." King City is 1 hr. from Monterey Peninsula and 3 hrs. from San Francisco. Excellent fringe benefits, opportunity to join Corp. after 6-12 months. Send CV or contact: Allan L. Fisher, MD, or Lee S. Roberts, Administrator, at Southern Monterey County Medical Group (A professional Corporation), 210 Canal St., King City, CA 93930, (408) 385-5471.

KING CITY, MONTEREY COUNTY, CALIFORNIA: "STEINBECK COUNTRY"—8-man multispecialty group is looking for 2 Family Practitioners-FP's must be willing to take OB's. Ability to speak Spanish helpful but not mandatory. King City is located 1 hr. from Monterey Peninsula and 3 hrs. from San Francisco. Excellent fringe benefits, 1st year guaranteed minimum salary, opportunity to join corporation after 6-12 months. Send CV or contact: Allan L. Fisher, MD, or Lee S. Roberts, Admin. SoMoCo Medical Group, 210 Canal St., King City, CA 93930, or telephone (408) 385-5471.

YUBA CITY-MARYSVILLE—Outstanding opportunity for medical practice. Office in established professional building for lease. Growing area. Reasonable terms. Call collect Gayla Stallins (916) 674-1330.

CALIFORNIA: Faculty member for Family Practice Residency Program located in Orange County. Prefer Residency trained, Board Certified Family Physician. Practice and/or teaching experience preferred. Responsibilities include In-Patient coordination of Residency Program or Out-Patient teaching activities. Salary negotiable. Program affiliated with University of Southern California, School of Medicine. Send all inquiries and CV to: Raymond Jones, MD, Chairman, Search Committee, 1200 North Tustin Ave., Suite 260, Santa Ana, CA 92705. Phone: (714) 547-5404.

SAN FRANCISCO KAISER-PERMANENTE MEDICAL CENTER. Full-Time Temporary Internist needed immediately for General Medical duties. Call collect—Dr. Fessell, (415) 929-4740.

SAN FRANCISCO BAY AREA: Three-man Family Practice group seek recent board-certified Family Practitioner for busy office. Attractive salary plus incentive, full fringes, 6 weeks vacation, and C.M.E. Send résumé to Philip R. Hines, MD, Inc., 220 Hospital Dr., Vallejo, CA 94590.

(Continued on Page 31)

FHP is Growing...

Grow with us!

We have opportunities in our multi-specialty group HMO in Salt Lake City for:

Family Physicians
Obstetrician / Gynecologists

For more information, contact:
Ralph Brown (801) 355-1234

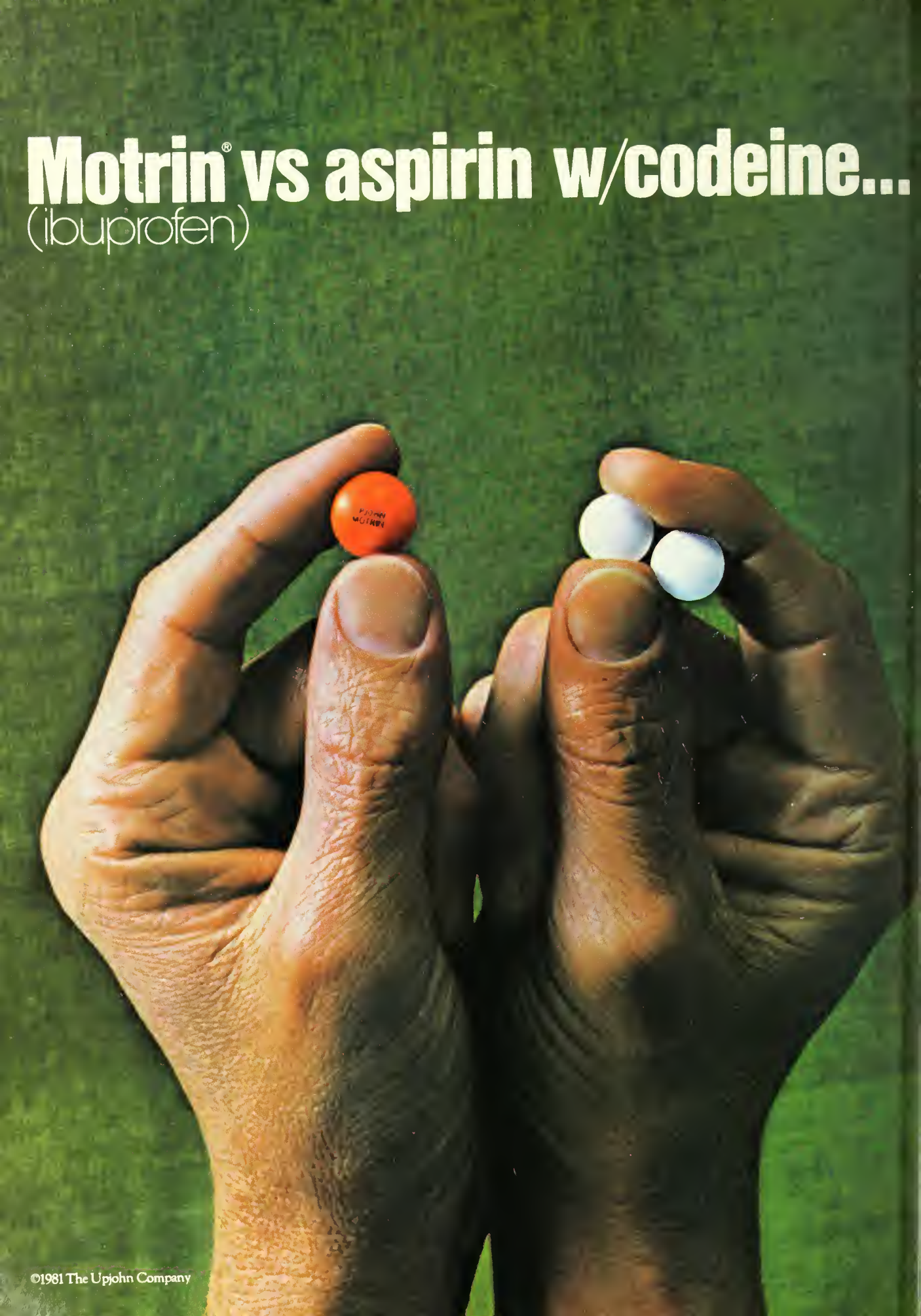
323 South 600 East. Salt Lake City. Utah 84102

DEVELOPMENTAL DISABILITIES PROGRAMS

Opportunities are available for internists, family practitioners and psychiatrists to work with developmentally disabled people in State residential communities. Locations from Los Angeles to northern California. Challenging and varied cases, congenial professional environment, excellent civil service benefits.

Hospital Recruitment Program
Dept. of Developmental Services
714 P Street
Sacramento, CA 95814
(916) 322-1221 collect

Motrin® vs aspirin w/codeine...
(ibuprofen)

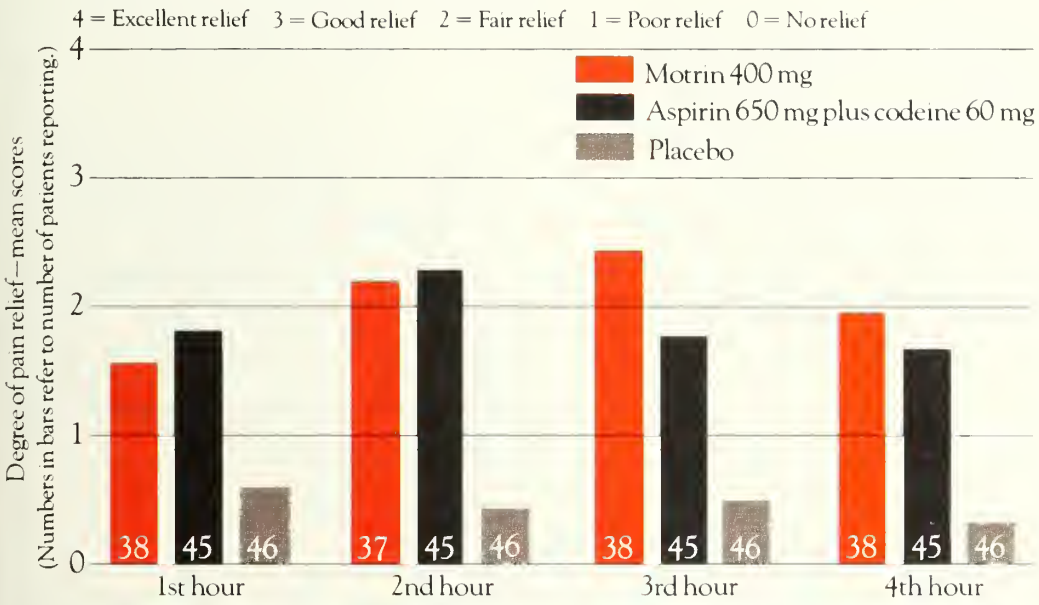


©1981 The Upjohn Company

compare the analgesic effect

A *Motrin* 400 mg dose relieved postsurgical dental pain as effectively as a combination of 650 mg aspirin and 60 mg codeine (two aspirin-with-codeine No. 3 tablets) in a study of 129 patients. In this double-blind, placebo-controlled, randomized study, no statistically significant difference in relief of pain was noted at 1, 2, and 4 hours between the *Motrin* and aspirin-with-codeine groups... with *Motrin* being significantly more effective ($p = 0.03$) at the three-hour interval. Active treatment was significantly more effective ($p < 0.0001$) than placebo at all time intervals.

Comparison of pain relief
Motrin vs aspirin-codeine combination



Data on file at The Upjohn Company.

One tablet q4-6h prn
For relief of mild to moderate pain:

Motrin® 400 mg TABLETS
ibuprofen, Upjohn

• Not a narcotic • Not addictive • Not habit forming • Nonscheduled • Acts peripherally • Relieves pain rapidly • Relieves inflammation • Indicated in acute and chronic pain • Well tolerated (The most common side effect with *Motrin* is mild gastrointestinal disturbance.)

Please turn the page for a brief summary of prescribing information.

Upjohn

Motrin® (ibuprofen) now proved an effective analgesic for mild to moderate pain

Motrin® Tablets (ibuprofen, Upjohn)

Indications and Usage: Relief of mild to moderate pain.

Treatment of signs and symptoms of rheumatoid arthritis and osteoarthritis during acute flares and in long-term management. Safety and efficacy have not been established in Functional Class IV rheumatoid arthritis.

Contraindications: Individuals hypersensitive to it, or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents (see WARNINGS).

Warnings: Anaphylactoid reactions have occurred in patients with aspirin hypersensitivity (see CONTRAINDICATIONS).

Peptic ulceration and gastrointestinal bleeding, sometimes severe, have been reported. Ulceration, perforation, and bleeding may end fatally. An association has not been established. Motrin should be given under close supervision to patients with a history of upper gastrointestinal tract disease, only after consulting ADVERSE REACTIONS.

In patients with active peptic ulcer and active rheumatoid arthritis, nonulcerogenic drugs, such as gold, should be tried. If Motrin must be given, the patient should be under close supervision for signs of ulcer perforation or gastrointestinal bleeding.

Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue Motrin and the patient should have an ophthalmologic examination, including central visual fields.

Fluid retention and edema have been associated with Motrin; use with caution in patients with a history of cardiac decompensation.

Motrin can inhibit platelet aggregation and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients should report signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

To avoid exacerbation of disease or adrenal insufficiency, patients on prolonged corticosteroid therapy should have therapy tapered slowly when Motrin is added.

Drug interactions. *Aspirin:* Used concomitantly may decrease Motrin blood levels. *Coumarin:* Bleeding has been reported in patients taking Motrin and coumarin.

Pregnancy and nursing mothers: Motrin should not be taken during pregnancy nor by nursing mothers.

Adverse Reactions

Incidence greater than 1%

Gastrointestinal: The most frequent type of adverse reaction occurring with Motrin is gastrointestinal (4% to 16%). This includes nausea;* epigastric pain;* heartburn;* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of the GI tract (bloating and flatulence). **Central Nervous System:** Dizziness;* headache, nervousness. **Dermatologic:** Rash* (including maculopapular type), pruritus. **Special Senses:** Tinnitus. **Metabolic:** Decreased appetite, edema, fluid retention. Fluid retention generally responds promptly to drug discontinuation (see PRECAUTIONS).

*Incidence 3% to 9%.

Incidence less than 1 in 100

Gastrointestinal: Upper GI ulcer with bleeding and/or perforation, hemorrhage, melena. **Central Nervous System:** Depression, insomnia. **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme. **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure. **Special Senses:** Amblyopia (see PRECAUTIONS). **Hematologic:** Leukopenia, decreased hemoglobin and hematocrit.

Causal relationship unknown

Gastrointestinal: Hepatitis, jaundice, abnormal liver function. **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities. **Dermatologic:** Alopecia, Stevens-Johnson syndrome. **Special Senses:** Conjunctivitis, diplopia, optic neuritis. **Hematologic:** Hemolytic anemia, thrombocytopenia, granulocytopenia, bleeding episodes. **Allergic:** Fever, serum sickness, lupus erythematosus syndrome. **Endocrine:** Gynecomastia, hypoglycemia. **Cardiovascular:** Arrhythmias. **Renal:** Decreased creatinine clearance, polyuria, azotemia.

Overdosage: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine, so alkaline diuresis may be beneficial.

Dosage and Administration: Rheumatoid arthritis and osteoarthritis, including flares of chronic disease: Suggested dosage is 300, 400, or 600 mg t.i.d. or q.i.d. Mild to moderate pain: 400 mg every 4 to 6 hours as necessary for relief of pain.

Do not exceed 2400 mg per day.

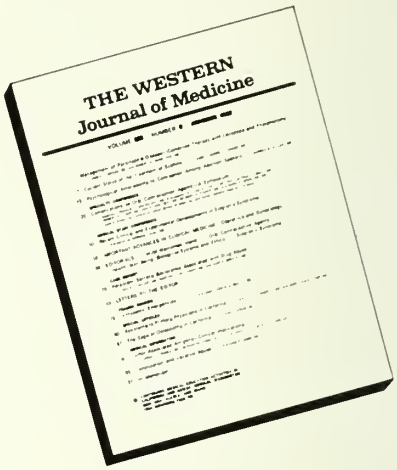
Caution: Federal law prohibits dispensing without prescription.

For additional product information, see your Upjohn representative or consult the package insert.

Upjohn THE UPJOHN COMPANY
Kalamazoo, Michigan 49001 USA

MED B-4-S

THE WESTERN Journal of Medicine



The cross-specialty clinical journal from the West

Please mail this coupon with enclosed payment to:
THE WESTERN JOURNAL OF MEDICINE
Circulation Department
731 Market Street
San Francisco 94103

Subscriptions:
U.S. and Canada $10 **Foreign $18**

WJ4/81

Enclosed is $ _____ to cover _____ subscriptions.
Regular ☐ Foreign ☐

Send subscription

TO: _____

_____
street

_____
city state zip

_____
specialty

Gift card to read

"From _____"

(Continued from Page 27)

PHYSICIAN WANTED

OPPORTUNITY FOR A BOARD CERTIFIED/QUALIFIED INTERNIST in San Diego area. Retiring physician with two younger associates in expense-sharing group desires replacement to assume existing practice in growing area. Gerald W. Ondash, MD, 105 Durian St., Vista, CA 92083. Telephone (714) 726-5722.

IDAHO—FAMILY PRACTICE. Three Physician Clinic, Opening 6/1/81, University Community. Salary Negotiable, Contact D. E. Adams, MD, Moscow Clinic, P.A., Moscow, ID 83843. Tel. (208) 882-7565.

ORTHOPEDIC SURGEON to join multispecialty group in Mt. Vernon, Washington. The Medical Center has outstanding x-ray facilities and is located across the street from a 126-bed hospital. Stockholder status available after one year. Guaranteed first year salary and liberal fringe benefits. On call coverage available. Position currently availabe. Contact Shane Spray, Administrator, Skagit Valley Medical Center, 1400 E. Kincaid, Mt. Vernon, WA 98273. Telephone (206) 428-2524.

INTERNAL MEDICINE—OREGON. Fastest growing community on Oregon Coast looking for 1-2 internists to join existing medical staff of 7 FP's and 1 surgeon. Excellent recreation opportunities—hunting, fishing, boating, etc. 47-bed hospital is 1¼ hours away from 400-bed medical center. Beautiful location. 12,000 population service area. Contact Doug Kunsman, Administrator, Western Lane Hospital, P.O. Box 580, Florence, OR 97439. (503) 997-3468.

PHYSICIAN WANTED: Green Valley, Arizona, satellite clinic looking for Board Certified or Board Eligible Family Practitioner to join one other Family Practitioner. Minimum 5 years experience preferred. Office practice only. Excellent income and fringe benefits. Reply to Box 6189, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

FINANCIAL REWARDS
and
PROFESSIONAL SATISFACTION . . .
. . . plus a whole lot more, Doctor!

We offer physician salaries in all specialties including General Practitioner and Family Practitioner that are among the highest paid in the nation and our benefit package (including malpractice insurance) is unexcelled.

Our quality of care is excellent; our medical facilities are attractive and efficient; and our climate for both living and working is outstanding.

We are one of the largest Federally-approved HMO's in the U.S., and we currently have a few very desirable positions available in the Los Angeles area. If you are interested, please call or write:

INA HEALTH PLAN OF CALIFORNIA
1880 Century Park East
Los Angeles, CA 90067
Phone (213) 553-6677, Extension 364
Attn.: Mr. Yoakam
Director of Physician Services

PHYSICIANS WANTED

INDUSTRIAL PHYSICIAN—In the heart of the Rockies. National Company seeking MD or DO with emphasis in general or internal medicine. Prefer Board Certified in Occupational Medicine. Responsibilities will include employee physicals, routine and emergency treatment of injuries and providing assistance in health maintenance and education program for Company employees. Forty-hour work week with generous benefits and compensation package. Excellent outdoor recreation opportunities abundantly available. Send CV to: Employment (WJM-MN), EG&G Idaho, Inc., P.O. Box 1625, Idaho Falls, ID 83415. Equal Opportunity Employer M/F/H/V. U.S. citizenship required.

PHYSICIANS WANTED

INTERNAL MEDICINE—FACULTY POSITION, Fresno, California. The Valley Medical Center of Fresno, in affiliation with the University of California San Francisco School of Medicine, is searching for a general internist to join the faculty of its Family Practice Residency Program. Responsibilities will include in-patient ward rounds and outpatient clinical instruction of housestaff and medical students, in departments of Family Medicine and Internal Medicine. Opportunities for clinical investigation, health services research, primary care curriculum development. Faculty practice plan offers attractive salary arrangements. The Valley Medical Center (440 beds) is the principal teaching hospital (total housestaff of 140) of a new clinical branch which the UCSF School of Medicine has established in the Fresno-central San Joaquin area of California. Kindly send C.V. with first letter of inquiry to: H. John Blossom, MD, Chief of Family Practice, Valley Medical Center, 445 S. Cedar Ave., Fresno, CA 93702.

DIRECTOR OF STUDENT HEALTH SERVICES, California State University, Fresno, twelve month position, appointment effective August 17, 1981, or earlier. Qualifications: valid license to practice medicine in the State of California, five years progressively responsible medical experience with at least one year's experience in administration; ability to direct and supervise a university student health service, as well as treat students. University with enrollment of 15,500 located in metropolitan area of 350,000 population within easy driving distance of Sierras and Pacific. Salary: $4,203-$5,090/month. Applicants should send vitae to: William Corcoran, Dean of Student Affairs, California State University, Fresno, Fresno, CA 93740; telephone (209) 487-2541. Application deadline: April 30, 1981. An Affirmative Action/Equal Opportunity Employer.

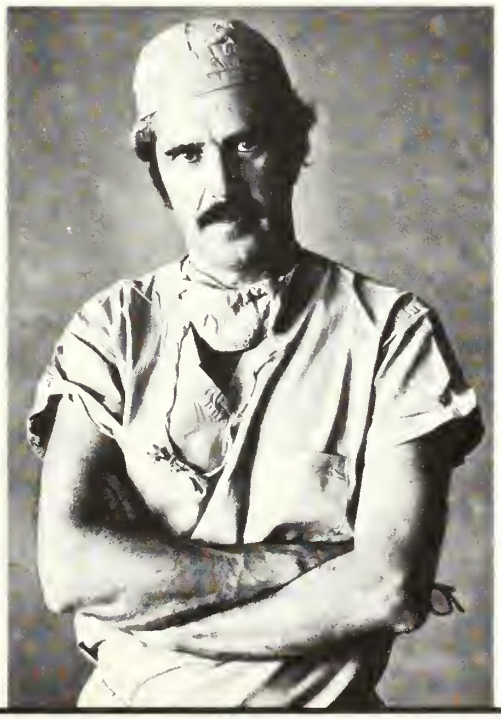
(Continued on Page 34)

We've taken the pain out of establishing your practice.

As a physician you're familiar with ways to alleviate pain. But chances are, your extensive educational process has not prepared you to handle the problems of selecting a location and establishing a successful private practice. National Medical Enterprises' Professional Relations Department has a staff of highly trained people who can help take the anguish out of making this important decision.

If you are familiar with NME you know us as one of America's largest and fastest growing health care companies that owns, operates, and manages acute care facilities that meet or exceed JCAH standards.

NME can provide Board Eligible/Board Certified physicians with private practice opportunities from Seattle, Washington to St. Petersburg, Florida - opportunities that enable you to concentrate on medicine while we assist you through the start-up phase of your new practice.



NME can offer you some of the best equipped health care facilities in the nation along with modern offices, a diverse choice of climates and a community ideally suited to your lifestyle.

Let us take the pain out of establishing a practice for you. Write and send us your curriculum vitae. Let us know your interests and where you want to live and practice. For additional information, contact:

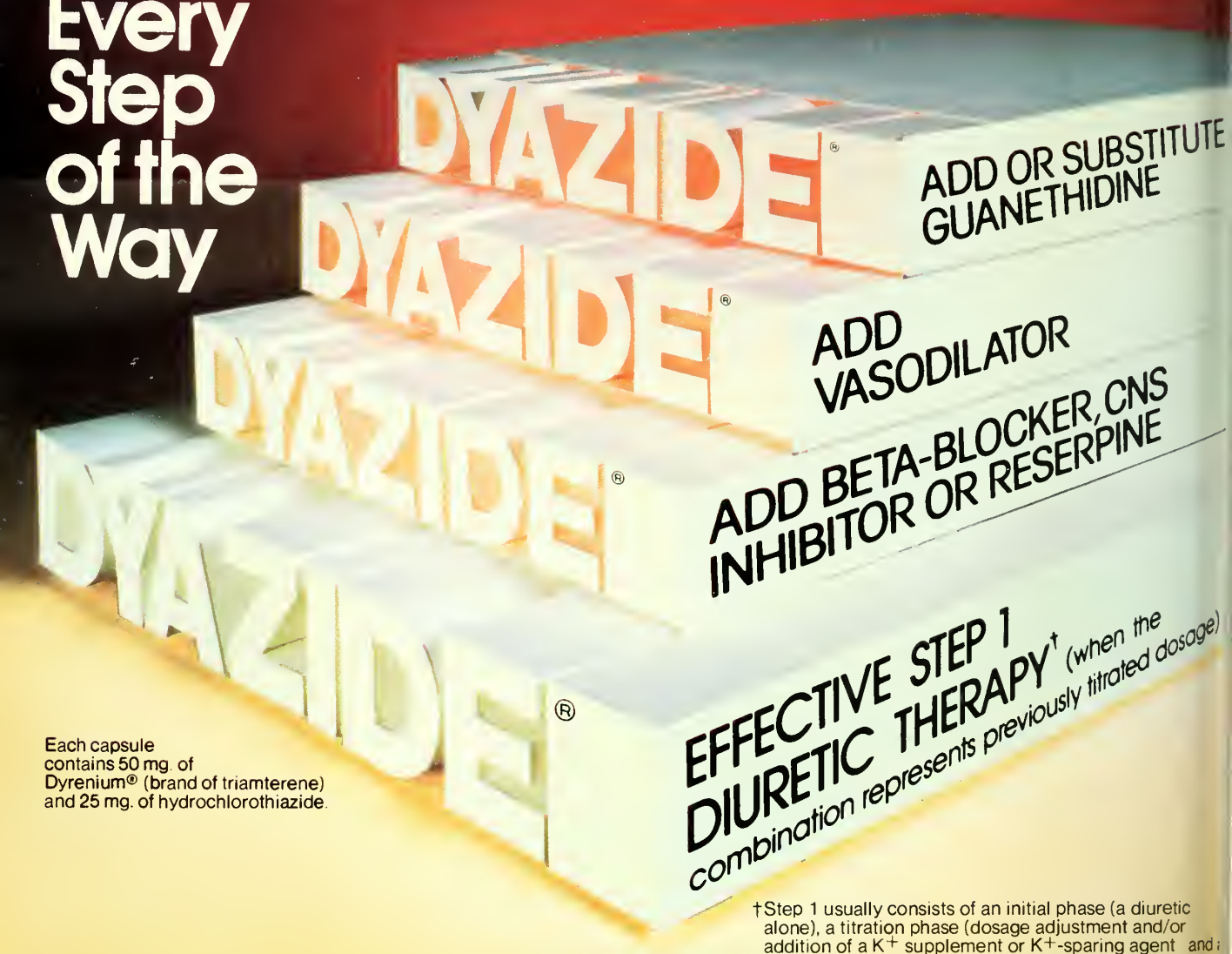
Raymond C. Pruitt
Director, Physician Relations
National Medical Enterprises
11620 Wilshire Blvd.
Los Angeles, California 90025
(213) 479-5526
1-800-421-7470

nme NATIONAL MEDICAL ENTERPRISES, INC.

"The total health care company."

In Hypertension*...When You Need to Conserve K^+

Every Step of the Way



Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

†Step 1 usually consists of an initial phase (a diuretic alone), a titration phase (dosage adjustment and/or addition of a K^+ supplement or K^+-sparing agent and a maintenance phase (a diuretic alone or in combination with a K^+ supplement or K^+-sparing agent).

Serum K^+ and BUN should be checked periodically (see Warnings).

Before prescribing, see complete prescribing information in SK&F Co. literature or *PDR*. A brief summary follows:

* **WARNING**
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K^+ frequently; both can cause K^+ retention and elevated serum K^+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in postsympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia, although uncommon, has been reported. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components.

Supplied: Bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

© SK&F Co., 1980

SK&F CO.
a SmithKline company
Carolina, P.R. 00630

THE WESTERN
Journal of Medicine

Refer to: Burt TB, Nelson JA: Extrahepatic biliary duct trauma—A spectrum of injuries. West J Med 134:283-289, Apr 1981

Extrahepatic Biliary Duct Trauma

A Spectrum of Injuries

TODD B. BURT, MD, *and* JAMES A. NELSON, MD, *Salt Lake City*

Blunt traumatic injury of the extrahepatic bile ducts (EBD) is uncommon. Familiarity with the wide spectrum of possible EBD injuries is essential, however, because of the increasing number of nonpenetrating abdominal injuries seen in modern society. These injuries include contusion with edema, hematoma and varying degrees of laceration. Edema and hematoma can result in transient bile duct obstruction that clears spontaneously or cicatrizing inflammatory reaction resulting in stricture and obstruction. Common bile duct stricture following blunt trauma is extremely rare, but is an unfortunate late complication requiring biliary decompression to relieve progressive jaundice. Laceration (partial or complete) can occur at any location in the EBD and can be life-threatening if the diagnosis is overlooked. Hemobilia is an unusual complication of laceration of the EBD. Failure to recognize the clinical manifestations of these uncommon injuries results in delayed and often incorrect diagnoses. Percutaneous transhepatic cholangiography is a safe and accurate procedure that is an important step in the workup of jaundice following blunt trauma.

EXTRAHEPATIC BILE DUCT (EBD) injury from blunt abdominal trauma (such as motor vehicle accidents or acts of violence) is uncommon. Severe injuries, such as laceration or transection require immediate surgical intervention to assure patient survival. Injuries that are less obvious clinically, including contusion with edema, hematoma from intramural and retroperitoneal hemorrhage and low-volume hemobilia, may be easily overlooked particularly in patients suffering from multiple trauma.

From the Department of Radiology, University of Utah College of Medicine, Salt Lake City.

Submitted July 25, 1980.

Reprint requests to: Todd B. Burt, MD, Department of Radiology, University of Utah Medical Center, 50 North Medical Drive, Salt Lake City, UT 84132.

Posttraumatic obstructive jaundice is an unfortunate sequela to EBD injuries. We report two cases of jaundice resulting from obstruction of the common bile duct following blunt trauma. In one case obstruction was caused by duodenal hematoma and edema which eventually cleared spontaneously. In the other case retroperitoneal and paraduodenal hematoma was followed by fibrosis resulting in stricture that required surgical bypass. Although upper gastrointestinal (GI) barium studies suggested the diagnosis and ultrasound testing showed bile duct dilatation, the site and gross nature of the obstruction was best demonstrated by thin-needle percutaneous transhepatic cholangiography (PTC). Our experience

ABBREVIATIONS USED IN TEXT

EBD = extrahepatic bile ducts
GI = gastrointestinal
LD = lactate dehydrogenase
PTC = percutaneous transhepatic cholangiography

with these two unusual cases prompted this report and a review of the literature.

Reports of Cases

CASE 1. A healthy 20-year-old woman sustained blunt trauma to her right upper abdomen from the steering wheel in a head-on auto accident. Although the patient had considerable right upper abdomen pain, there was no evidence of acute abdomen or blood loss. Liver function test findings and amylase determinations were normal except for mildly elevated levels of lactate dehydrogenase (LD). After a three-day stay in hospital the patient was discharged with only a complaint of mild pain of the right upper quadrant. Two and one half weeks later, the patient returned, complaining of persistent right upper abdomen pain, nausea and the recent onset of brownish-colored urine. She stated that she had not been exposed to hepatitis, blood transfusion, alcohol or intravenously given drugs. On physical examination, yellowish discoloration of skin and striking scleral icterus were noted. Findings of an abdominal examination were normal except for mild right upper quadrant tenderness. Significant laboratory findings included the following: total bilirubin 12.2 and direct bilirubin 9.6 mg per dl, alkaline phosphatase 228 units, LD 222 units and SGOT (serum aspartate aminotransferase; formerly serum glutamic oxaloacetic transaminase) 131 units. Amylase, a complete blood count, prothrombin time and partial thromboplastin time were within normal limits.

The patient was admitted to hospital and a liver-spleen scan using technetium 99m sulphur colloid showed a liver and spleen without defect. An upper GI study suggested an intraduodenal hematoma in the second portion of the C-loop (Figure 1). An ultrasound test showed mildly enlarged gallbladder and extrahepatic bile ducts. PTC was done with a 23-gauge Chiba needle on the third hospital day. This demonstrated a normal intrahepatic biliary tree with obstruction of the distal common bile duct by a persistent, smooth-mass effect with failure to empty into the duodenum. Follow-up films at one hour showed persistent contrast in the biliary tree (Figure 2).

Figure 1.—Upper gastrointestinal barium study showing narrowing and irregularity in the second portion of the duodenum **(arrow)** that suggests hematoma or edema.

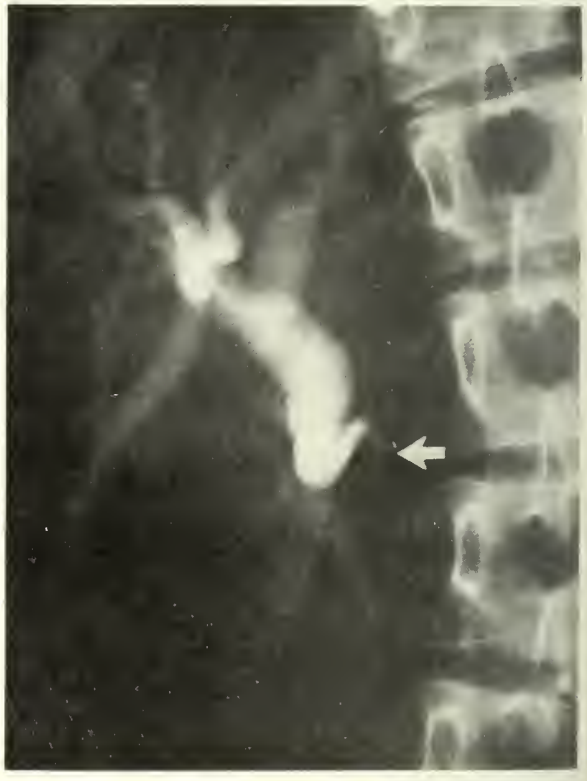


Figure 2.—One hour follow-up film after thin-needle percutaneous transhepatic cholangiography. Tapered distal common duct with meniscal obstruction **(small arrow)** and no passage of contrast into duodenum. Excretory urograms from contrast entering vascular system from obstructed biliary system.

Because of symptomatic improvement it was elected to only observe the patient. Over the next several months the patient's jaundice gradually subsided without surgical intervention and all symptoms resolved. Two years following the accident, the patient was asymptomatic with normal findings on liver function tests.

CASE 2. A 22-year-old man sustained a crush injury to the upper abdomen in a drilling accident. An exploratory laparotomy was done immediately because of grossly bloody peritoneal tap. During the operation hematomas involving the second and third portions of the duodenum, the retroperitoneal space and the posterior aspect of the pancreas were found. The gallbladder was intact and there was no evidence of bile duct laceration or transection. The hematomas were drained and the patient was later discharged with abdominal wounds healing well and normal findings on liver function tests except for mildly elevated LD levels.

The patient was readmitted approximately three weeks later for persistent nausea, vomiting, a 25-pound weight loss, and increasing malaise and weakness. An upper GI study was done, which showed compression of the duodenum by hematoma or fibrosis (Figure 3). Abdominal ultrasound testing demonstrated a normal pancreas, and no dilated biliary ducts were seen. During this hospital stay the patient was noted to have scleral icterus. Laboratory results included total bilirubin 5.2 mg per dl, alkaline phosphatase 504 units and SGOT 141 units. PTC was done with a 23-gauge Chiba needle, which showed dilated hepatic and common bile ducts with complete distal obstruction (Figure 4). No intraluminal filling defects were present in the ducts or gallbladder. An operation was carried out immediately following the PTC and massive adhesions in the area of the duodenum, gallbladder and liver bed were discovered. Pronounced fibrosis and thickening were present in the periampullary region, but no residual hematomas were found.

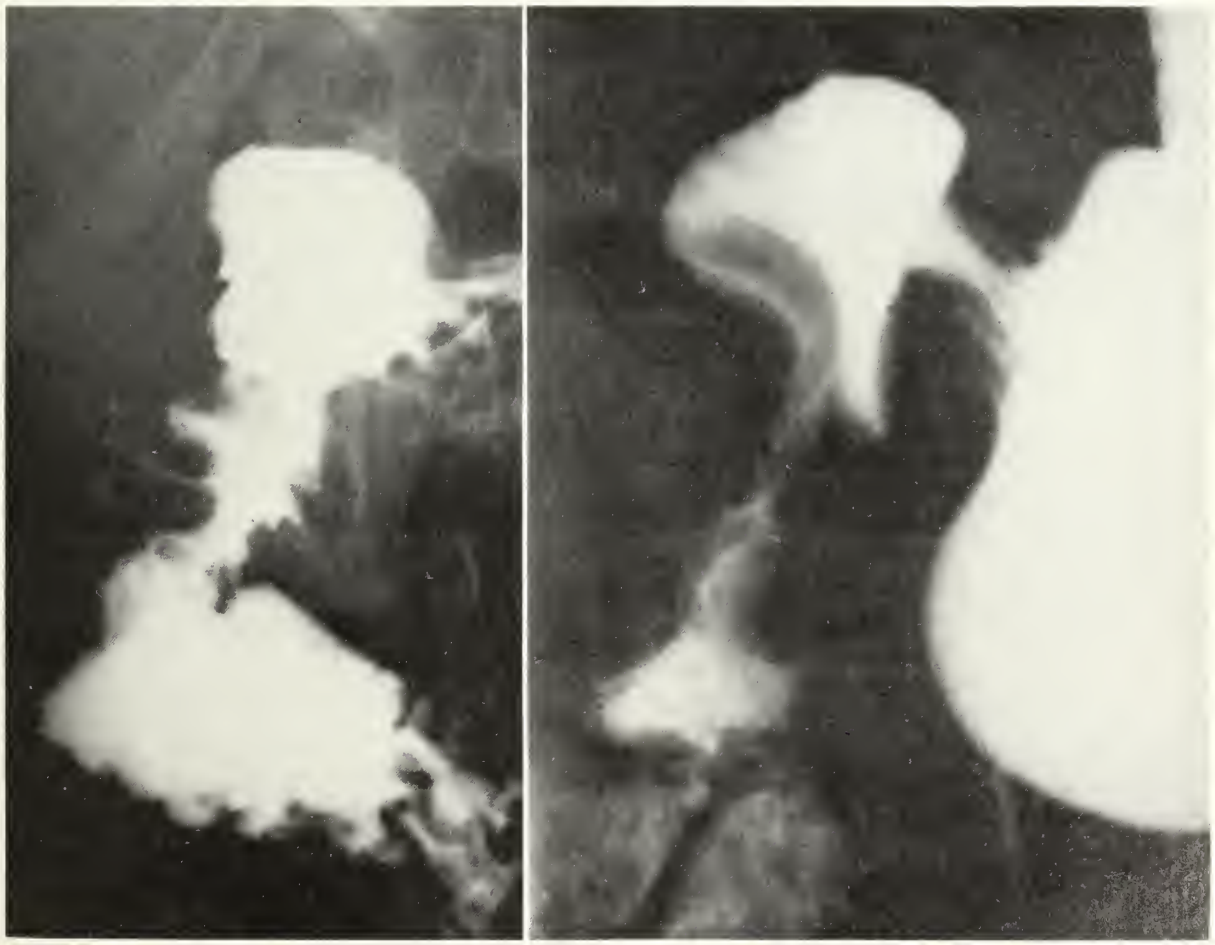


Figure 3.—Two views from upper gastrointestinal study showing irregularity and narrowing involving the second and third portion of duodenum, which proved secondary to massive adhesions.

Surgical decompression with T-tube drainage was carried out and the patient's liver function gradually improved and symptoms slowly resolved. However, because of persistent obstruction noted on the follow-up T-tube cholangiograms, Roux-en-Y cholecystojejunostomy was done. The patient tolerated this procedure well, and his postoperative course was uncomplicated. During follow-up, findings of liver function tests returned to normal and all symptoms resolved.

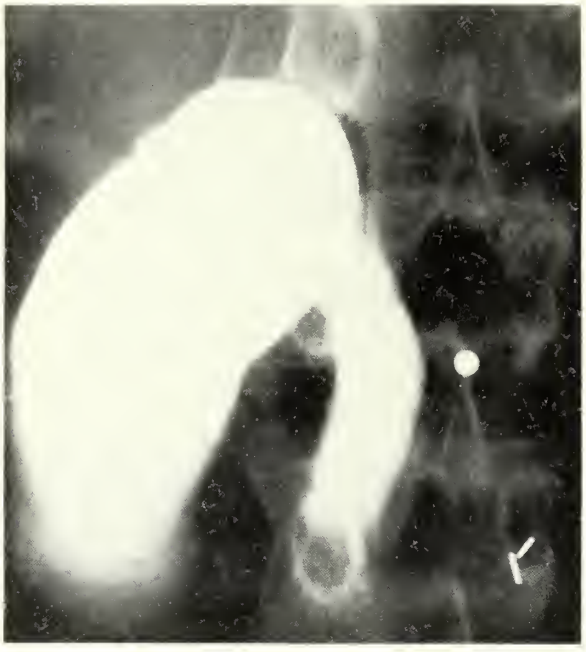


Figure 4.—PTC with injection into gall bladder shows dilated extrahepatic biliary ducts and abrupt obstruction of the distal common bile duct. The obstruction was secondary to pronounced fibrosis in the paraduodenal and retroperitoneal region (PTC = percutaneous transhepatic cholangiography).

TABLE 1.—*Causes of Jaundice Following Blunt Abdominal Trauma*

Trauma-related
Liver laceration
Liver hematoma
Liver abscess
Hepatic vascular accident
Budd-Chiari
Hemobilia
Acute pancreatitis
Posttraumatic hepatic dysfunction syndrome
Intrahepatic and extrahepatic duct damage
Posttraumatic cholecystitis
Surgery-related
Iatrogenic
Operative stress on preexisting liver disease
General anesthesia
Postoperative cholecystitis
Miscellaneous
Hemolysis (transfusions, resolving hematoma)
Viral hepatitis
Drug toxicity

Discussion

Jaundice Following Trauma

Jaundice is often a perplexing complication that develops following major abdominal trauma. Historical, clinical and laboratory data will often distinguish hemolytic, obstructive or hepatocellular causes of jaundice. Following traumatic injuries, however, many patients receive multiple blood transfusions, may have preexisting liver disease, and often undergo operations requiring general anesthesia. In these cases, the differential diagnosis may be difficult and easy differentiation becomes impossible. Some important causes of jaundice following blunt abdominal trauma are listed in Table 1.

Liver lacerations, hematomas, abscesses and vascular injuries may all result from blunt abdominal trauma and lead to jaundice.[1] Rarely, as illustrated in these two case reports, hematoma, edema, or both, and fibrosis can compress the distal common bile duct and result in temporary or permanent obstruction. Recently, the posttraumatic hepatic dysfunction syndrome has been described as a distinct clinicopathologic entity.[2] This syndrome is considered to result from hepatic ischemia caused by either hypoxia or hypotension following resuscitation from major trauma.

In a traumatized patient who has undergone an operation, mild hyperbilirubinemia in the first few postoperative days may be viewed with interest but without serious concern because many of these patients are suspected of having hemolysis from blood transfusions or from resorption of hematoma. If jaundice is persistent or progressive, however, iatrogenic surgical trauma to the biliary tree, anesthetic toxicity and operative stress on preexisting liver disease should be considered as potential causes.[1,3,4] Acute acalculous cholecystitis must also be considered because of its known occurrence in both traumatized and surgical patients.[5,6]

When obstructive jaundice is suspected, abdominal ultrasound testing and PTC are essential to arrive at the correct diagnosis. Ultrasonography is very helpful in demonstrating dilated biliary ducts, gallbladder and common bile duct stones, as well as abdominal hematomas, abscesses and cysts. However, ultrasound testing alone cannot diagnose an EBD laceration or indicate the site of

TABLE 2.—*EBD Rupture Due to Blunt Abdominal Trauma*

Type	*No. of Cases*	*No. of Deaths*
Transected common duct	25	7
Lacerated common duct	31	10
Transected hepatic duct	2	0
Lacerated hepatic duct	27	10
Lacerated cystic duct	1	0
Unknown site	5	1
TOTAL	91	28

EBD = extrahepatic bile duct

an obstruction.[7] As illustrated in our case reports, PTC is a fast, accurate and safe method for differentiating obstructive from nonobstructive jaundice and for defining the level of obstruction when present. PTC may also show extravasation secondary to either a liver or biliary tree laceration, intraluminal filling defects secondary to either blood clots or stones, or deviation of the biliary ducts from abscess or hematoma.

Pathophysiology of EBD Injuries

The exact nature of the force necessary to cause injury to the EBD is unknown, although the following have been postulated: (1) impingement and compression of the ductal system on the vertebral column,[8] (2) external compression of the gallbladder with transmitted rise in intraductal pressures resulting in "blowout of the duct"[9] and (3) laceration of the ductal system at the junction of its fixed and mobile portions.[10,11] The first theory seems to explain best the duct injuries that result in hematoma and edema, especially in the periampullary and retroperitoneal region. Injuries to the vessels supplying the EBD in this region result from the crushing abdominal blow and result in hematoma and ischemia which may heal with fibrosis. The last postulate best explains duct laceration and is clinically supported in that rupture of the EBD is most frequently encountered where the mobile common bile duct becomes fixed as it enters the superior edge of the pancreas.[12] The blowout theory has not been confirmed in animal models or in clinical situations.[13] Although the exact pathophysiology still remains unclear, it is likely that a combination of the mechanisms proposed above is responsible for EBD injuries.

The rarity of injury to the portal vein and hepatic artery has intrigued many writers. Dorton[14] suggested that the tortuous and elastic hepatic artery has no points of fixation near the area of trauma, making it less susceptible to injury. He also suggested that because the portal vein has no valves, intraluminal pressure from a direct blow is decompressed into the splenic reservoir, dissipating the energy.

Extrahepatic Biliary Duct Injuries

Complete and partial laceration occurring in all portions of the EBD have been previously described. A careful review of the literature from 1890 to 1970 by Rydell uncovered 91 cases of EBD lacerations.[12] Table 2 tabulates the location and degree of these ruptures. Since that time, avulsion of the ampulla of Vater,[15,16] as well as several other reports of EBD ruptures,[17-25] have been added to the literature. The most common location for duct disruption is the suprapancreatic retroduodenal portion (superior border of the pancreas.[1,17,22] Laceration may be limited to a single portion of the biliary tree[15,18,20,22,26] or may be found in combination with other EBD injuries.[21] EBD injuries may also be isolated or may be found in any combination with other abdominal visceral injuries with the liver, duodenum, pancreas, and spleen being the most common sites.[27] When distal common bile duct injuries occur, pancreatic and duodenal injuries are commonly associated.[16]

In severely injured patients, indications for exploratory laparotomy are often clearly evident and unsuspected biliary tract trauma may be found during the operation. When the abdominal injury is less severe or confined to the biliary tree, however, indications for laparotomy may not be present and a significant occult injury of the EBD may remain undiagnosed. Walt and Grifka[28] reported on 307 consecutive cases of blunt abdominal trauma and found that injuries to the common bile duct were the least frequent injury to result in exploratory laparotomy. To add to the difficulty in differential diagnosis, a history of trauma may not be given because the patient may either feel that it was insignificant or fail to recall it.

The clinical course of EBD lacerations has a characteristic pattern[20,22] as follows: (1) The initial injury may be followed by shock of varying degree that usually lasts for only a few hours; (2) this is often followed by a symptom-free quiescent period of several days; (3) finally, progressive abdominal pain, nausea, vomiting, jaundice and, in some cases, abdominal distention from bile ascites ensue. Acholic stools, fever, rapid wasting of abdominal muscles and scleral

icterus often develop as well. Although this sequence usually occurs over three to ten days, symptoms may not become intense enough to cause the patient to seek medical advice for weeks to months. Abdominal paracentesis may yield bile, at which time the diagnosis should be clear.[27]

Biliary duct obstruction resulting from edema or hematoma in the duodenal, periampullary or retroperitoneal region is uncommon. During the past 30 years more than 170 cases of intramural and paraduodenal hematomas from blunt abdominal trauma have been reported.[7,29-36] In only four of these previously cited cases did the hematoma result in obstruction of the distal common bile duct.[7,33-35] To these, we add an additional case, bringing the total to five. Of these cases, three patients did not recall abdominal trauma, one considered the traumatic episode minor and one had significant blunt trauma to the abdomen. This attests to the fact that a history of trauma is not always obtained even when a serious duodenal and retroperitoneal hematoma is present. In the previously reported and currently presented cases of biliary obstruction, one required decompression by cholecystojejunostomy,[33] two resolved after evacuation of the blood clot[34,35] and the other two resolved spontaneously (patients in reference 7 and in case 1). Jaundice developed as early as three days,[34] and as late as three weeks (case 1) following the traumatic episode. Davis[33] has suggested that the characteristic delay between injury and jaundice is secondary to gradual increase in the size of the hematoma. He postulates that as the hematoma undergoes proteolysis, tissue fluid is absorbed from the interstitial spaces by osmosis and results in delayed obstruction of the distal common bile duct.

Abdominal trauma may result in delayed obstruction of the common bile duct from fibrosis, as illustrated in our second case. This is extremely rare with only two other reported cases in the English literature.[37] These cases represent a more subtle type of duct injury than rupture or complete division. A small tear with subsequent bile leakage initially may not be evident clinically or at laparotomy. This may result in a small area of inflammation, followed by healing with fibrosis that results in stricture or complete obstruction. Another possibility is that paraduodenal hematoma may undergo organization with fibrosis and subsequent common duct stricture. As noted both in our case and a previously reported case, this injury was not observed at initial laparotomy despite mobilization of the head of the pancreas and duodenum. In all cases the biliary tree required permanent decompression by a Roux-en-Y choledochojejunostomy.

Another important, albeit unusual, complication of EBD injury is hemobilia. Sandblom reviewed 355 cases of hemobilia and found that 55 percent were secondary to trauma.[38(p53)] If caused by blunt trauma, the blow was usually extremely violent and often resulted in damage to several organs. He reported that most hemobilia resulted from parenchymal rupture of the liver and that out of 80 patients with blunt abdominal trauma

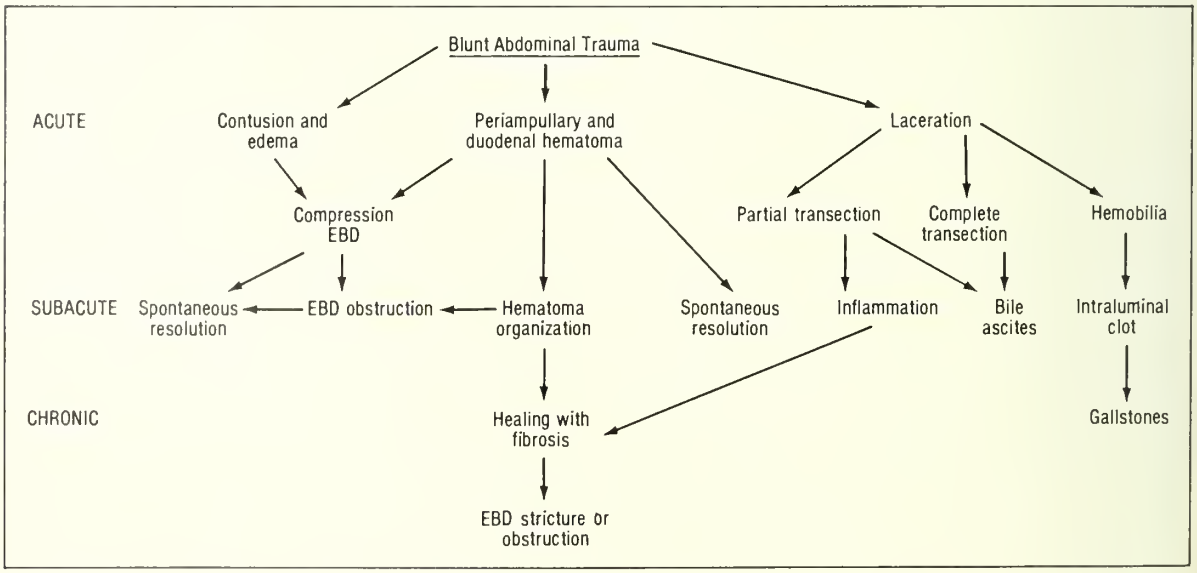


Figure 5.—EBD injuries and sequelae secondary to blunt abdominal trauma (EBD = extrahepatic bile ducts).

and hemobilia, only four originated from EBD injuries.[38(p6)] Hemobilia often develops following trauma, with the classic triad of biliary colic, jaundice and gastrointestinal bleeding. The pain, produced by the distention of the bile ducts with blood, precedes external evidence of bleeding, so that a patient with recurrent episodes of bleeding may be able to predict the onset of melana or hematemesis. Arteriography is diagnostic when hemorrhaging is actually occurring; intermittency of bleeding, however, is characteristic of hemobilia. A related complication of theoretic interest is the formation of gall stones from intraluminal clots, which has been demonstrated by Sandblom.[39] The incidence of this condition is unknown but is undoubtedly rare.

Surprisingly, no reports of posttraumatic EBD fistulae or cysts were encountered in the literature. Bronchobiliary and pleurobiliary fistulae, however, have been reported from intrahepatic ducts to the chest after severe thoracic and abdominal trauma.[40]

Conclusion

Extrahepatic bile duct trauma may clearly result in a wide spectrum of injuries as summarized in Figure 5. Although these injuries are uncommon, clinicians as well as radiologists must be thoroughly aware of their existence in order to provide adequate care for these traumatized patients. Abdominal ultrasound and GI studies will often suggest an EBD injury, which can be safely and directly demonstrated by PTC. Treatment of EBD laceration and transection is clearly surgical.[22] When trauma results in edema or hematoma, however, therapy must be based on the condition of the individual patient and consideration of other abdominal injuries.[29]

REFERENCES

1. Hardy JD: Postoperative jaundice, *In* Sabiston DC (Ed): Textbook of Surgery, 11th Ed. Philadelphia, Saunders, 1977, pp 429-430

2. Champion HR, Jones RT, Trump BF, et al: Post-traumatic hepatic dysfunction as a major etiology in post-traumatic jaundice. J Trauma 16:650-657, 1976

3. Seror J, Schmitt JC, Pateras C, et al: Operative injuries to the bile ducts. Int Surg 63:108-113, 1978

4. Hillis TM, Westbrook KC, Caldwell FT, et al: Surgical injury of the common bile duct. Am J Surg 134:712-716, 1977

5. Howard RJ, Velany JP: Postoperative cholecystitis. Am J Dig Dis 17:213-218, 1972

6. Dupriest RW: Acute cholecystitis complicating trauma. Ann Surg 189:84-89, 1979

7. Foley CL, Teele RL: Ultrasound of epigastric injuries after blunt trauma. AJR 132:593-598, 1979

8. Lewis KM: Traumatic rupture of the bile duct. Ann Surg 108:237-241, 1938

9. Mason LB, Sidnury JB, Guiang S: Rupture of the extrahepatic ducts from non-penetrating trauma. Ann Surg 140:234-241, 1954

10. Mohardt JH: Traumatic rupture of the common bile duct. Q Bull NW Med Sch 30:16-20, 1956

11. Fish JC, Johnson GL: Rupture of the duodenum following blunt trauma. Ann Surg 162:917-919, 1965

12. Rydell WB: Complete transection of the common bile duct due to blunt abdominal trauma. Arch Surg 100:724-728, 1970

13. Fletcher WS, Mahnke DE, Dunphy JE: Complete division of the common bile duct due to blunt abdominal trauma. J Trauma 1:87-95, 1961

14. Darton HE: Complete division of the common bile duct due to blunt abdominal trauma. Am Surg 31:331-335, 1965

15. Parkinson SW, Wisniewski ZS: Avulsion of the ampulla of Vater: An isolated injury following blunt abdominal trauma. Aust NZ J Surg 48:562-564, 1978

16. Balsano NA, Reynolds BM: Rupture of the common duct and ampulla of Vater due to blunt trauma. Ann Surg 178:200-203, 1973

17. Tonnesen P: Rupture of extra-hepatic biliary ducts from blunt external trauma. Dan Med Bull 17:238-245, 1970

18. Janss G, Freimark L: Isolated transection of the common duct. JACEP 8:161-163, 1979

19. Sinclair MC, Moore TC, Asch MJ, et al: Injury to hollow abdominal viscera from blunt trauma in children and adolescents. Am J Surg 128:693-698, 1974

20. Shorthouse AJ, Singh MP, Treasure T, et al: Isolated complete transection of the common bile duct by blunt abdominal trauma. Br J Surg 65:543-545, 1978

21. Zollinger RM, Keller RT, Hubay CA: Traumatic rupture of the right and left hepatic ducts. J Trauma 12:563-569, 1972

22. Turney WH, Lee JP, Raju S: Complete transection of the common bile duct due to blunt trauma. Ann Surg 179:440-444, 1974

23. Parkinson SW: Complete severance of the common bile duct due to blunt trauma. Aust NZ J Surg 39:253-254, 1970

24. Caro AM, Losa JMO: Complete avulsion of the common bile duct as a result of blunt abdominal trauma. J Pediatr Surg 5:60-62, 1970

25. Haynes CD, Given KS, Stone HH, et al: Nonsurgical trauma to the extrahepatic ducts. South Med J 62:1323-1326, 1969

26. Moffat RC, Lucas RJ: Transection of the common bile duct as an isolated injury following blunt trauma. Can J Surg 12:334-335, 1969

27. Longmire WP, McArthur MS: Occult injuries of the liver, bile duct, and pancreas after blunt abdominal trauma. Am J Surg 125:661-666, 1973

28. Walt AJ, Grifka TJ: Blunt abdominal injury, *In* Gurdjian ES, Lange WA, Patrick LM, et al (Eds): Impact Injury and Crash Protection. Springfield, IL, Charles C Thomas, 1970, pp 101-123

29. Fullen WD, Selle JG, Whitely DH, et al: Intramural duodenal hematoma. Ann Surg 179:549-555, 1974

30. Maull KI, Fallahzudeh H, Mays ET: Selective management of posttraumatic obstructing intramural hematoma of the duodenum. Surg Gynecol Obstet 146:221-224, 1978

31. Izant RF, Drucker WR: Duodenal obstruction due to intramural hematoma in children. J Trauma 4:797-813, 1963

32. Resnicoff SA, Morton JH: Changing concepts concerning intramural duodenal hematomas. J Trauma 9:561-576, 1969

33. Davis DR, Thomas CY: Intramural hematoma of the duodenum and jejunum. Ann Surg 153:394-398, 1961

34. Parrish RA, Edmondson HT, Moretz WH: Duodenal and biliary obstruction secondary to intramural hematoma. Am J Surg 108:428-430, 1964

35. Ferguson IA, Goade WJ: Intramural hematoma of the duodenum. N Engl J Med 260:1176-1177, 1954

36. Felson B, Levin ET: Intramural hematoma of the duodenum: A diagnostic sign. Radiology 63:823-831, 1954

37. Skow JR, Longmire WP: Common duct stricture secondary to blunt abdominal trauma. Ann Surg 40:576-578, 1974

38. Sandblom P: Hemobilia (Biliary Tract Hemorrhage), 1st Ed. Springfield, IL, Charles C Thomas, 1972

39. Sandblom P, Mirkovitch U, Saegesser F: Formation and fate of fibrin clots in the biliary tree. Ann Surg 185:356-366, 1977

40. Operal SS, Mandal AK: Traumatic thoracobiliary fistulae: Clinical and review study. J Trauma 18:539-544, 1978

Refer to: Salz JJ: Recent advances in cataract operations—Phacoemulsification, intraocular lens implantation and prolonged-wear soft contact lenses. West J Med 134:290-295, Apr 1981

Recent Advances in Cataract Operations

Phacoemulsification, Intraocular Lens Implantation and Prolonged-Wear Soft Contact Lenses

JAMES J. SALZ, MD, *Los Angeles*

A standard cataract extraction involves removal of the entire cataractous lens through a 12- to 13-mm incision with the aid of a cryoprobe while phacoemulsification consists of removing the cataract through a 3-mm incision by breaking the lens into small pieces with an ultrasonically vibrating needle which is then used to aspirate the fragmented cataract. Most ophthalmic surgeons choose to carry out the standard cataract extraction because although phacoemulsification offers a more rapid rehabilitation due to smaller incisions, it requires special training and experience and expensive, complicated equipment.

Once the cataract is removed, vision can be restored with strong cataract glasses, contact lenses or intraocular lens implants. Cataract glasses are the safest but produce a magnified image. Contact lenses produce more normal vision but are often difficult to handle. Intraocular lenses offer the most normal vision but are accompanied by an increased risk of complications.

TO UNDERSTAND the differences between the standard cataract extraction and phacoemulsification, a brief description of the anatomy of a typical cataract is necessary. The cataractous lens consists primarily of the three structures: the capsule, the cortex and the nucleus (Figure 1). The nucleus is the central core of the lens. It is usually relatively soft in 40- to 50-year-old patients with a cataract, moderately firm in cataract patients in their 60's and usually quite hard in those 70 years old and beyond. As the cataract progresses, the nucleus changes from clear to yellow to dark brown. Surrounding the central nucleus is the lens cortex. In a mature or *ripe* cataract, the lens cortex is milky white; in an immature cataract, it is relatively clear. Often the cortex forms opaque plaques along the posterior lens capsule (Figure 1). Surrounding the soft lens cortex is the lens capsule, which is the outermost layer of the lens. The capsule consists of the anterior capsule and the posterior capsule, which join at the equator of the lens.

From the Department of Ophthalmology, Los Angeles County/University of Southern California Medical Center, Los Angeles.

Submitted, revised, October 20, 1980.

Reprint requests to: James J. Salz, MD, 8631 W. Third Street, Suite 800, Los Angeles, CA 90048.

Intracapsular Cataract Extraction

During the 1950's and 1960's, most ophthalmologists carried out basically the same operation on patients in need of cataract operations. The surgical procedure is called intracapsular cataract extraction and consists of the removal of the entire lens (Figure 2). In brief, the procedure

consists of making a 160° to 180° incision (usually about 10 to 12 mm) along the superior limbus (junction of the cornea and sclera). A freezing probe is applied to the lens capsule while the cornea is retracted and the entire cataractous lens is then withdrawn through the pupil and out of the eye. The incision is closed with very fine sutures. This operation has been and still is today, a highly successful procedure which gives excellent results. Because it has been so successful over the years, it remains the method preferred by most ophthalmic surgeons in the United States.

Phacoemulsification

In the early 1970's, Dr. Charles Kelman of New York City introduced an ingenious but controversial new method for the removal of senile cataracts called phacoemulsification (Figure 3). In this technique, a 3-mm incision is made at the superior limbus and a tiny sharp hook is then used to tear a large opening in the anterior lens capsule. A small aspirating needle capable of rapid ultrasonic vibration is then introduced into the incision to make contact with the hardened lens nucleus. With short bursts of ultrasonic vibration, the needle emulsifies the formed lens nucleus into small particles, which are then aspirated through the opening in the tip of the needle. Once the nucleus is removed, another probe tip is used to aspirate the remaining cloudy lens cortex. The posterior lens capsule can be left intact but, because of a tendency to late opacification, a central 4- to 5-mm opening is often made in the center of the posterior capsule to assure a clear optical axis.

Many patients confuse phacoemulsification with laser treatment, and they may say they want to have their cataracts removed "without surgery." Laser energy cannot be used to remove cataracts and the phacoemulsification technique is definitely a surgical procedure.

The principal advantage of phacoemulsification is the small incision which can usually be closed with one or two sutures. Theoretically, this allows for more rapid rehabilitation of the patient. In

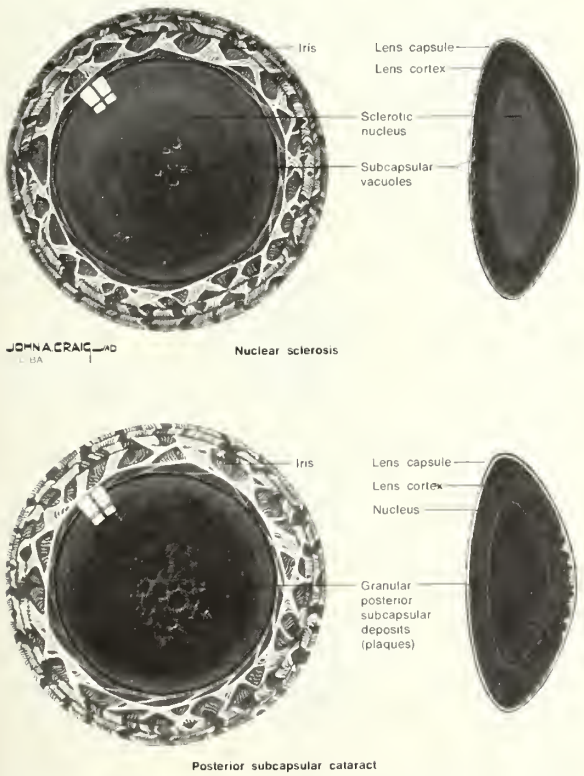


Figure 1.—Types of senescent (senile) cataracts. (© Copyright 1974 CIBA Pharmaceutical Company, Division of CIBA-GEIGY Corporation. Reprinted with permission from CLINICAL SYMPOSIA illustrated by John A. Craig, MD. All rights reserved.)

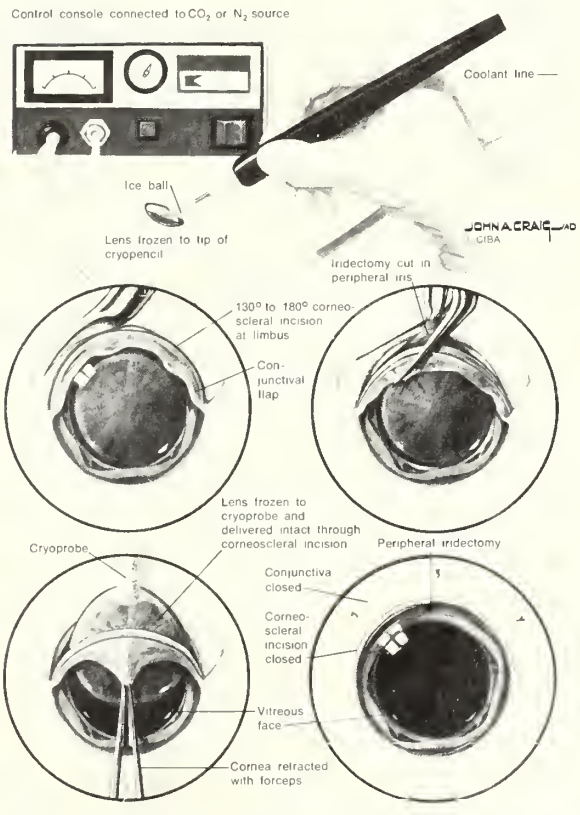


Figure 2.—Cryoextraction method of cataract removal. (© Copyright 1974 CIBA Pharmaceutical Company, Division of CIBA-GEIGY Corporation. Reprinted with permission from CLINICAL SYMPOSIA illustrated by John A. Craig, MD. All rights reserved.)

actual practice, because of the fine suturing technique done under the operating microscope, even the patient who has had intracapsular cataract extraction can recover much more rapidly than in the past. In the average elderly patient with a cataract, postoperative rehabilitation would be quite similar regardless of which of these two techniques were used. Proponents of phacoemulsification feel the technique may be associated with a slightly lower incidence of postoperative retinal detachment and macular edema, but this has yet to be proved.

Disadvantages of the phacoemulsification technique include the cost and complexity of the equipment and the delicate nature of the operation itself. The phaco unit costs approximately $30,000, and for good results the technique requires special training and practice even for a skilled surgeon. Proper patient selection is also critical during a surgeon's early experience with the phaco procedure.

Further discussion of the pros and cons of these two methods of cataract extraction is beyond the scope of this paper. Suffice to say that in the hands of skilled surgeons, both techniques can yield excellent and comparable results, and either technique can have potential advantages or disadvantages for a given patient.

An increasingly popular alternative to phacoemulsification is planned extracapsular cataract extraction. This involves enlarging the incision to 10 mm, expressing the lens nucleus and removing the residual cortex with the irrigation and aspiration handpiece.

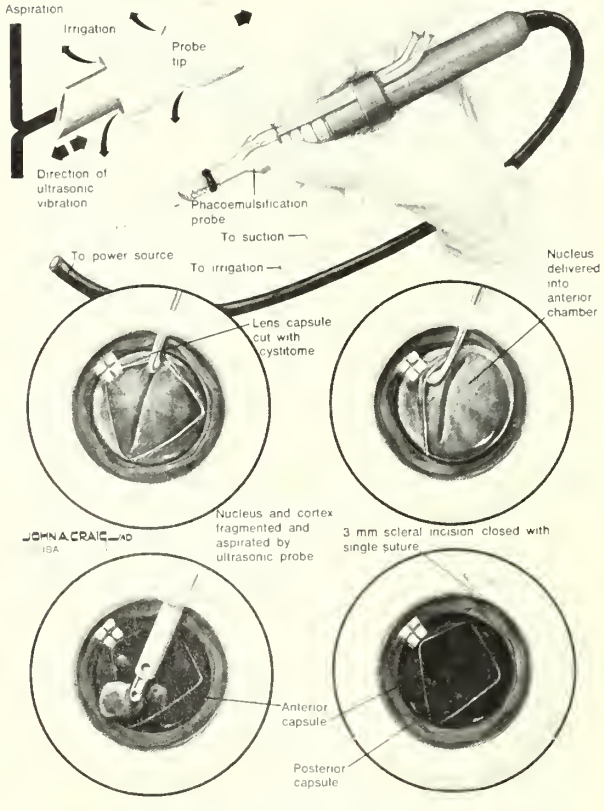


Figure 3.—Phacoemulsification method of cataract removal. (© Copyright 1974 CIBA Pharmaceutical Company, Division of CIBA-GEIGY Corporation. Reprinted with permission from CLINICAL SYMPOSIA illustrated by John A. Craig, MD. All rights reserved.)

Indications for Cataract Operations

When to remove the cataract is important. It must be remembered that cataracts very rarely have to be removed for medical reasons. In the extremely rare case where a cataract is causing a secondary glaucoma or a severe inflammatory reaction in the eye, then it must be removed for the well-being of the eye. In most cases, however, the cataract does not have to be removed until the patient has significant complaints about impaired vision and feels that this impairment is interfering with his or her life-style or visual requirements. The degree of decreased vision caused by the cataract should be enough that it makes it difficult for the patient to drive or read or, perhaps, to carry out activities that he or she treasures. The idea that the cataract is now "ready" even when the patient has no significant visual complaint or that it is better to remove the cataract early, as if it were a form of malignancy, should alert the patient to seek another opinion.

Restoration of Vision

Perhaps even more controversial than the introduction of phacoemulsification in the early 1970's has been the increasing popularity of intraocular lens implantation, which began in the mid 1970's. Because the benefits of the intraocular lens implants are strictly optical, a brief explanation of the decision facing a cataract patient is in order. After the cataract is removed, the eye is aphakic and receives a blurred image (except in those rare instances where the eye has been extremely myopic before the development of the cataract). The methods of refocusing this blurred image are cataract glasses, contact lenses and intraocular lens implants.

Cataract Glasses

Cataract glasses can refocus an aphakic eye and, in the presence of a healthy retina and optic

nerve, will usually restore close to 20/20 vision. Although this sounds good on the surface, this type of 20/20 vision is different from the vision the patient may have had before the cataracts developed. Because cataract glasses consist of strong-powered (approximately +12.00) lenses in a frame about 12 mm in front of the eyes, a magnification effect of approximately 25 percent to 30 percent is created (Figure 4, lower E). Because objects appear larger, they also appear closer than they really are. Thus, the patient may have some difficulty with depth perception. Also, because the cataract glasses must be relatively thick to achieve the necessary power, the edges of the lenses may cause optical aberration. This aberration may interfere with the patient's peripheral vision and make driving and walking difficult, although many patients gradually adjust to these changes.

If the patient has a significant cataract in one eye and very little cataract in the other eye, it will not be possible for him or her to wear cataract glasses. The magnification effect created by the lens in front of the aphakic eye makes fusion of the image formed by the normal eye impossible, and the patient experiences a form of diplopia caused by the difference in image size (Figure 4, middle and lower E).

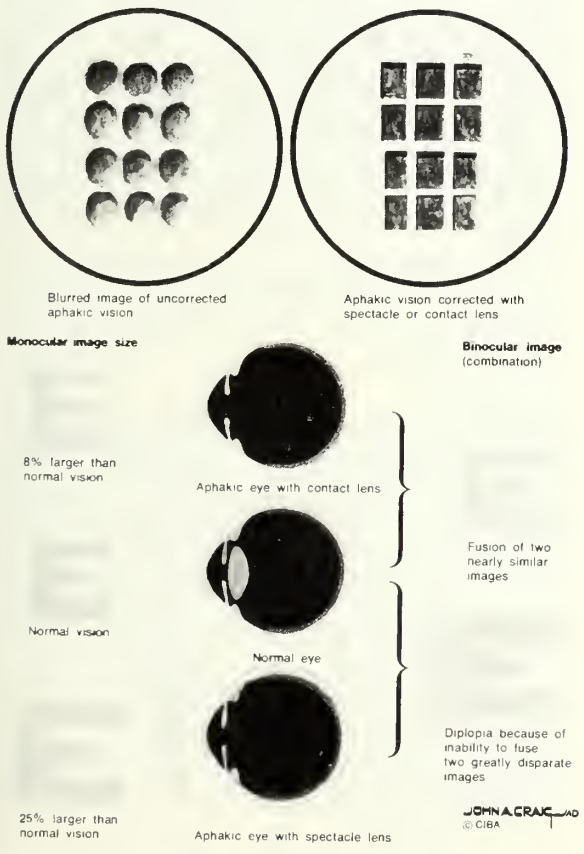


Figure 4.—Aphakic vision. (© Copyright 1974 CIBA Pharmaceutical Company, Division of CIBA-GEIGY Corporation. Reprinted with permission from CLINICAL SYMPOSIA illustrated by John A. Craig, MD. All rights reserved.)

Contact Lenses

Contact lenses are optically superior to even the newest types of cataract glasses. Because the contact lens rests on the surface of the cornea, the magnification effect is reduced to only about 8 percent to 10 percent and the peripheral vision is near normal (Figure 4, top E). Unfortunately, many of the patients in the cataract age group find it difficult or impossible to master insertion and removal of the contact lens.

The newer prolonged-wear soft contact lenses recently approved by the Food and Drug Administration (FDA) eliminate the need to handle the lenses. However, approximately 30 percent to 40 percent of aphakic patients who try the lenses overnight or longer eventually fail for one reason or another.[1-3] Those that are successful require frequent office visits for cleaning and replacement of the lenses, and this can be a burden. The infection rate with these lenses is higher than in patients who remove their lenses daily, and the potential for a serious corneal ulcer is created because the bandage effect of the soft lens can keep the eye relatively comfortable even in the presence of a serious ulcer. However, these soft lenses can be extremely successful and many patients have worn them for over four years. They are indicated primarily in patients for whom an implant is contraindicated and as an alternative to cataract glasses in patients who are already aphakic. The lenses should be tried as an alternative to a secondary lens implant in patients with aphakia.

Intraocular Lens Implants

As stated previously, the only advantage the intraocular lens implant provides the patient is an optical one. Although there are minor variations among implant styles, because all of them are inside the eye, the implants are positioned very close to the point from which the cataract was removed. In Figure 4, the lens implant would be placed very close to the position of the normal lens as shown in the normal eye (middle diagram). This practically eliminates any

magnification effect and assures more normal peripheral vision. It is also a good alternative for patients who have an advanced cataract in one eye and normal or near-normal vision in the other eye. The eye with the implanted lens will focus very well with the normal eye, thus providing better restoration of a patient's binocular vision and depth perception. Although the intraocular lens can provide the most normal restoration of vision, it has created a controversy in the ophthalmic community; however, more and more ophthalmologists are finding this an acceptable procedure. Thus, lens implants seem to have come of age.

The early work in lens implantation was done in England by Ridley and Choyce,[4] and in Holland by Binkhorst.[5] There are hundreds of patients in Europe who have had intraocular lenses implanted in the eye as long as 20 years ago. The vast majority of these patients have tolerated the procedure without serious complications.

In the United States, however, with the exception of a few surgeons who did lens implantations in the 1960's, renewed interest in this procedure did not occur until the mid 1970's. It quickly became apparent that interest in the procedure outstripped the technical ability of US manufacturers to supply the lenses, and some of the early lens implants were not properly designed or manufactured. Unfortunately, this led to an unacceptably high rate of complications with certain lens designs. Because of these complications and the lack of long-term follow-up, the Food and Drug Administration has classified the lens as an investigational device.

Implant Styles

A brief description of the three methods of lens implantation follows; however, a discussion of the advantages or disadvantages of these methods is beyond the scope of this paper.

Anterior Chamber Lens

Anterior chamber lens implants have the optical portion of the implant in front of the pupil and are fixated by tucking the edges of the lens into the "angle" of the eye just above the peripheral iris. This implant is usually easily visualized in the eye by shining a light into the area of the pupil from the temporal side (see Figure 5).

Pupillary Lens

Pupillary lenses have the optical portion of the implant in the plane of the iris and are fixated by the iris. Again, the implant can be visualized by shining a light across the pupil from the temporal side. Some pupillary lenses can be dislocated by dilating the pupil, so dilation to examine the fundus should not be done unless the situation has been discussed with the patient's ophthalmologist. A dislocated lens can present a serious problem, both to the patient and to the ophthalmologist (see Figure 6).

Posterior Chamber Lens

Posterior chamber lenses have the optical portion behind the iris and are fixated by the ciliary body and the posterior lens capsule. These implants can only be visualized by the slit lamp. With the hand light, the eye will look perfectly

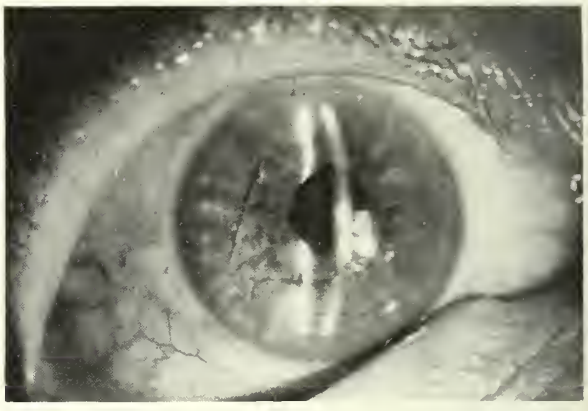


Figure 5.—Anterior chamber implant (one year following operation). The slightly blurred vertical slit beam of light to the right is on the cornea. The focused beam of light to the left is on the lens implant and iris. The implant is fixated in front of the iris and pupil.

Figure 6.—Pupillary supported implant (five years following operation). The vertical beam of light to the right is on the cornea. The implant is supported by the iris. The superior back loop of the implant can be visualized disappearing under the iris at the upper edge of the pupil and is again visible in the iridectomy at 12 o'clock.

normal and it may be difficult to tell that the patient had had a cataract operation (see Figure 7).

Risks of Intraocular Lens Implants

At the American Academy of Ophthalmology Meeting in San Francisco in November 1979 the preliminary results of the FDA study were reported.[6] The data presented involved 177,503 lens implants done between February 1978 and August 1979. Although the study is not final, this preliminary report indicated that in the short term, the incidence of complications among implant patients and the control group were similar. When completed, the FDA study will be impressive because of the vast number of patients and physicians involved. At present, the study has had a relatively short follow-up period. There are reports, in the literature, however, by Binkhorst[5] and Choyce[4] that detail a very favorable experience with lens implantation with follow-up periods of greater than ten years.

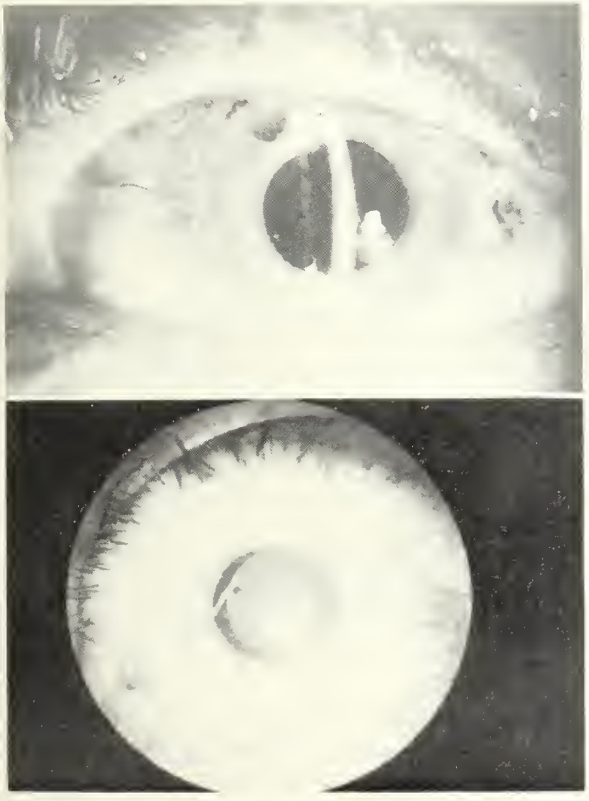


Figure 7.—Posterior chamber implant (six days following operation). The broad vertical beam of light to the right is on the cornea. The faint beam of light to the left is on the surface of the implant and this beam is striking a small hole in the implant just inside the lower edge of the pupil. This hole is used to aid in positioning the implant in the eye and would be invisible in an undilated pupil. The implant and its supporting loops are all behind the iris. With a more widely dilated pupil, the entire optical portion of the implant lens, the two positioning holes and a portion of one of the supporting Prolene loops become visible.

Because of these generally acceptable results in large numbers of patients, it is my opinion that the risk/benefit doctrine should be applied when considering a patient for lens implantation. Admitting that there is a slightly greater risk of complications when implanting an intraocular lens, is the benefit to the patient great enough to justify this slightly increased risk? In the patient with only one functioning eye, it is clearly not worth taking any added risks. So too, in an eye compromised by glaucoma, diabetic retinopathy or inflammation, it is clearly not worth taking the additional risk of implanting an intraocular lens which is, after all, still a foreign body to the eye. But in the average elderly patient with an otherwise healthy eye and with a potentially useful second eye, I believe that he or she has the right to achieve the optical advantage of the lens implant, thereby assuming the additional risk once all the facts are presented. This opinion is based on personal observations of the results of lens implantations in selected patients during the last five years.

Summary

Both intracapsular cataract operations and phacoemulsification are highly successful procedures for the removal of cataracts. Once the cataract is removed the eye must be refocused with cataract glasses, contact lens or a lens implant to restore visual function. The lens implant offers significant optical advantages but with some increase in risk. The desirability of removing the cataract should be based primarily on the patient's visual difficulties, which will vary considerably according to the patient's age, general health and occupation.

REFERENCES

1. Salz JJ, Schlanger JL: Prolonged wear soft contact lenses. Am Intra-Ocular Implant Soc J 6:246-248, Jul 1980

2. Phillips AJ: Extended wear hydrogen lenses in the United Kingdom. Int Contact Lens Clin Jan/Feb, 54, 1979

3. Kersley JH, Kerr C, Pierse D: Hydrophilic lenses for continuous wear in aphakia. Br J Ophthalmol 61:38, 1977

4. Choyce DP: The evolution of the anterior chamber implant up to and including the Choyce Mark IX. Ophthalmology 86: 197-206, Feb 1979

5. Binkhorst CD: The iridocapsular (two-loop) lens and the iris-clip (four-loop) lens in pseudophakia. Trans Am Ophthalmol Otolaryngol op 589-617, Sep-Oct 1973

6. Worthen DM: Interim F.D.A. report on intraocular lenses. Presented at the American Academy of Ophthalmology Meeting, San Francisco, Nov 7, 1979

Refer to: Moss AJ: Blood pressure in infants, children and adolescents (Medical Progress). West J Med 134:296-314, Apr 1981

Blood Pressure in Infants, Children and Adolescents

ARTHUR J. MOSS, MD, *Los Angeles*

In infants the flush and Doppler methods of blood pressure measurement are usually used. The flush method measures mean pressure; the Doppler method, systolic and diastolic pressures. Normal flush values from 1 to 12 months of age do not exceed 100 mm of mercury; Doppler systolic levels do not exceed 113 mm of mercury.

Data concerning normal limits for children and adolescents are conflicting. For practical purposes, a persistent pressure of 140 mm of mercury systolic or 90 mm of mercury diastolic in patients more than 10 years of age is indicative of hypertension. In those younger than 10 years, systolic pressure does not normally exceed 130 mm of mercury and diastolic pressure does not normally exceed 85 mm of mercury.

Primary hypertension is relatively infrequent in pediatric patients and diagnosis should be made with deliberation and caution. Antihypertensive drug therapy is indicated only for severe hypertension and in selected cases of moderate hypertension.

PRESENT EMPHASIS on hypertension and on its possible origin during childhood has served as a stimulus for physicians to measure blood pressure as a part of the routine pediatric physical examination. In patients who have been admitted to hospital, this is considered as important and routine as documentation of body temperature, pulse rate and respiratory rate. In patients seen in physicians' offices, it is now common practice to measure and record blood pressure in all children older than 2 or 3 years of age. In those younger than this age, measurement is not usually carried out unless a specific indication exists.

Blood pressure is a reflection of a number of hemodynamic variables including cardiac output, peripheral vascular resistance, blood volume and arterial elasticity. Therefore, readings considered to be abnormal have important implications and may form the basis for investigation of a variety of systems that can influence the level of blood pressure. Consequently, the *accuracy* of blood pressure measurement has assumed a position of primary importance. An error in one direction can lead to unnecessary and costly studies, whereas an error in the other direction can lead to neglect of an important underlying disorder. Of all medical procedures, measurement of blood pressure is one that perhaps is best ingrained in medical students; yet, even in this age of scientific preciseness, it is often recorded with little regard for accuracy.

Human and instrumental errors in the measurement of blood pressure are numerous. Although

From the Department of Pediatrics, UCLA School of Medicine, Los Angeles.

Reprint requests to: Arthur J. Moss, MD, Department of Pediatrics, UCLA Center for the Health Sciences, Los Angeles, CA 90024.

individually these errors may be relatively unimportant, collectively the resultant inaccuracy can be considerable. The indifferent and hurried manner in which blood pressure is often recorded clearly reflects failure on the part of the examiner to appreciate this.

Indirect measurement of blood pressure, even if accomplished with the utmost care, is still an estimate rather than a precise determination since a number of physical events, some of which can be neither controlled nor influenced, are in force. Even in the basal state, both systolic and diastolic pressures may vary significantly with the phase of respiration or the phase of blood flow. These differences are exaggerated by changes in the rate or rhythm of the heart, by deep breathing, Valsalva maneuver and the like. Also, systolic pressure varies diurnally with an early morning low point and an early evening high point. With the subject at complete rest the systolic pressure is decreased, and after meals there is a transient increase. Strong sensory stimuli arising from such things as a distended bladder, pain or physical activity are known to cause a rise in blood pressure. Fear, apprehension, agitation and other emotional factors also tend to raise arterial pressure. Exposure to cold may result in a lowering of pressure; whereas exposure to heat may cause an increase. Finally, periodic physiological undulations (Traube-Hering waves), possibly related to variations in vasomotor activity, respiratory movements, heart rate and stroke volume may account for fluctuations that can reach a magnitude as high as 40 mm of mercury in some persons.[1] All of these physiological variables are frustrating to examiners, but knowledge of them directs attention to the need for more than a single measurement as well as the importance of reducing extrinsic errors to a minimum.

Measurement of Blood Pressure—General Considerations

Patients, instruments, techniques of measurement and examiners may be sources of errors in measurement. Most of the problems can be alleviated or even completely controlled with proper care and patience on the part of the examiner.

Patients

As indicated earlier, the level of arterial pressure, both systolic and diastolic, may vary considerably with the phase of respiration or with changes in cardiovascular hemodynamics. Deep breathing, crying, laughing, anxiety, recent activity and abnormal body temperature exert profound influences. Thus, it is important to reassure patients (particularly children), and to allow time for recovery from anxiety or exercise. Body temperature must be considered in evaluation of the reading obtained. Since the state of relaxation is generally less stable in children than in adults, greater variation with consecutive measurements is often observed, particularly in those younger than 2 or 3 years old.

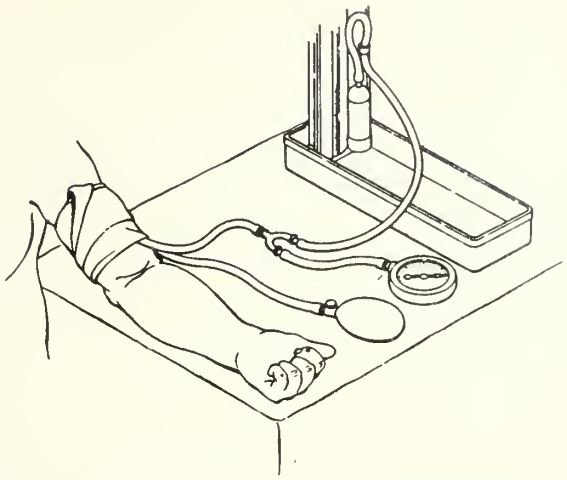


Figure 1.—Diagram illustrating a method for establishing the accuracy of an aneroid manometer. Pressure registrations are compared simultaneously with those of a mechanically perfect mercury mamometer by attaching the two manometers to a single arm cuff. (From Moss AJ, Adams FH: Problems of Blood Pressure in Childhood, 1962. Courtesy of Charles C Thomas, Publisher, Springfield, IL.)

Instruments

A common source of error is the instrument itself. In selecting a manometer, careful inspection for mechanical defects should be made. A mercury manometer is the sphygmomanometer of choice. Before use it should be inspected for leaks, improper valve function, dirty tubes and loss of mercury. The latter causes a displacement of the zero level.

An aneroid manometer is more compact but somewhat less accurate than a mercury manometer because mechanical hysteresis may cause a loss of linearity, resulting in gross inaccuracies. However, for all practical purposes, it is acceptable provided that it is checked periodically against a mechanically perfect mercury manometer. This is easily and quickly accomplished by comparing simultaneous registrations of pressure at different

levels on the two instruments connected by a Y tube to a single arm cuff (Figure 1).

Technique of Measurement

Certain precautions should become a matter of habit. The mercury column must be vertical, and the eye of the examiner should be at the level of the meniscus. It is important in infants and children to select a cuff of appropriate size. A cuff which is too narrow may result in error on the high side; whereas one which is too wide may result in error on the low side. Use of a narrow cuff requires a higher inflation pressure to compress the artery because of poor transmission. With use of a cuff that is too wide, a larger segment of the vessel must be compressed and this produces increased resistance to flow with the pulse tending to disappear before it reaches the lower edge of the cuff (Figure 2). Although a relatively precise index of proper cuff selection for a given child has been established,[2] for practical purposes it is sufficient merely to select a cuff that covers about two thirds of the upper arm length. There is evidence to suggest that a cuff that is too wide introduces little or even no error,[3] so if one is to err, it would probably be best to err on the wide side. The smallest cuff (2.5 cm) is known to introduce gross inaccuracies and, on rare occasions, may fail to occlude the underlying artery, even at the highest cuff pressure attainable. Its use is recommended only when the infant is so small that a larger cuff would encroach on the antecubital area.

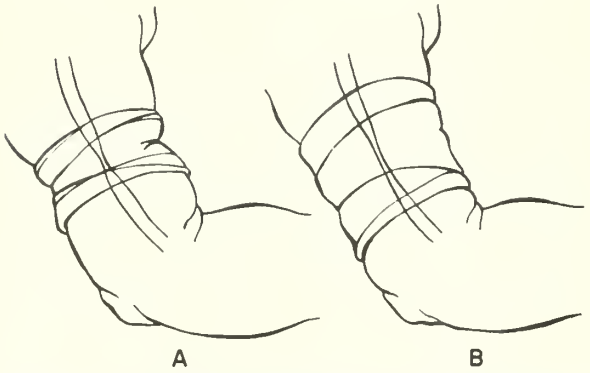


Figure 2.—A, Diagram showing the effect of an arm cuff that is too narrow. This results in poor transmission of the pressure to the underlying artery. The manometer reading in such a case is higher than the pressure which actually exists within the vessel. **B,** When a cuff of proper width is used, the pressure is effectively transmitted to the underlying artery and more accurate readings are obtained. (From Moss AJ, Adams FH: Problems of Blood Pressure in Childhood, 1962. Courtesy of Charles C Thomas, Publisher, Springfield, IL.)

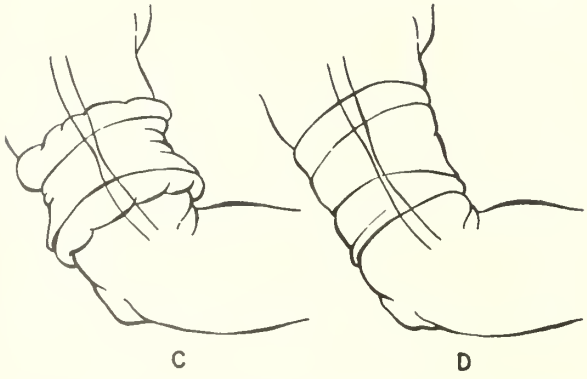


Figure 3.—C, Diagram showing the effect of a loosely applied arm cuff. With inflation, a ballooning of the cuff occurs, and the effective surface is narrowed. The manometer reading in this case is higher than that which actually exists within the vessel. **D,** When the cuff is snugly applied, ballooning does not occur, and the effective surface is not altered. (From Moss AJ, Adams FH: Problems of Blood Pressure in Childhood, 1962. Courtesy of Charles C Thomas, Publisher, Springfield, IL.)

The proper *length* of the inflatable bag within the cuff has not been established. In accordance with recommendations of The American Heart Association,[4] it should be at least long enough to halfway encircle the extremity with care taken to apply the bag directly over the artery. Some[3] believe that it must completely encircle the limb, whereas others[5] believe that the length of the bag is relatively unimportant. A bag that completely or almost completely encircles the limb is probably preferable.

Data are also lacking regarding the appropriate size of cuff for measurement of blood pressure in the leg. At present, selection of a leg cuff is without scientific basis. Here again, it is probably better to err on the side of too wide a cuff rather than too narrow a cuff. The common impression that arterial pressure is higher in the legs than in the arms is a misconception and probably reflects use of cuffs of inadequate width.[6,7]

The cuff must be applied *snugly* to the bare limb. A loosely applied cuff causes ballooning of the bag with narrowing of the effective cuff surface in contact with the tissues (Figure 3). This results in a recorded arterial pressure that is erroneously high.

The cuff should be inflated rapidly and deflated slowly—at a rate of 3 to 5 mm of mercury per second. Too rapid deflation can result in errors in either direction. Low readings occur when the rate of deflation is so fast that the different phases of

the vascular sounds cannot be accurately interpreted. High values are obtained when the rapid rate of deflation causes a negative pressure above the mercury column, preventing equalization of pressure in the cuff and in the manometer tube.

Whenever possible, sufficient time should be allowed for recovery from anxiety, meals or activity. Children may be placed in either a sitting or recumbent position. Theoretically, if the vasomotor reflexes are intact and active, it should make little difference whether the patient is sitting or recumbent. Recumbent measurements should be made if the sitting pressure is abnormally high and vice versa. Regardless of the position of the patient, the arm should be perfectly relaxed in a position of slight flexion and abduction. In the sitting position, the forearm should be supported on a smooth surface *at the level of the heart* (Figure 4).

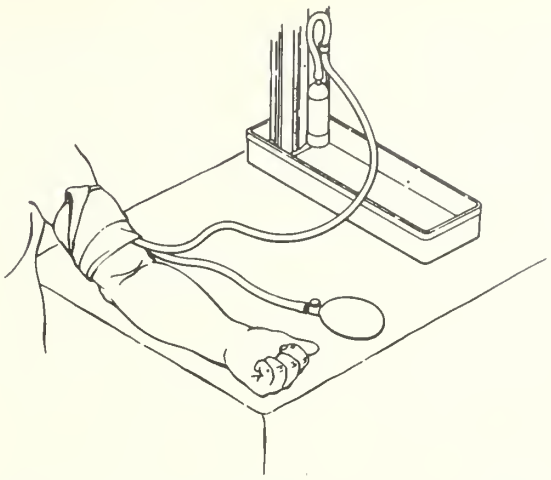


Figure 4.—Diagram showing arm position and sphygmomanometer cuff application. The cuff should be applied evenly and snugly about the bared arm, the lower edge being about one inch above the antecubital space. The forearm should be in a position of slight flexion and abduction and must be at the level of the heart. (From Moss AJ, Adams FH: Problems of Blood Pressure in Childhood, 1962. Courtesy of Charles C Thomas, Publisher, Springfield, IL.)

The Examiner

It is recommended that two or three readings of systolic and diastolic pressure be recorded. If the examiner suffers auditory impairment, an electronic stethoscope may be helpful for measurement by the auscultatory method. Determination of blood pressure can be entrusted to personnel other than physicians if they have had proper instructions and sufficient experience.

It is not generally appreciated that many observers introduce a subjective digit error. Studies have shown that there is a great preference for zero as the terminal digit.[8]

Blood Pressure Measurement in Children and Adolescents

In this age group, as in adults, blood pressure measurements customarily are registered by auscultation. With this method, it is often helpful to locate the artery in the antecubital fossa by palpation after the cuff is applied but before it is inflated. The head of the stethoscope should be firmly applied but not in contact with the lower edge of the cuff.

As indicated earlier, the cuff should be *deflated* slowly. *Inflation,* however, must be rapid since slow inflation may result in a period between systole and diastole during which all vascular sounds disappear (auscultatory gap).[9] The auscultatory gap may result in a profound error in interpretation of either systolic or diastolic pressure.

With cuff inflation above the peak pressure of the arterial pulse wave, the artery is completely occluded and there are no audible sounds. With gradual deflation, the vessel opens, the pressure pulse is transmitted to the periphery and the vascular sounds of Korotkoff appear. These occur in four identifiable phases: the sudden appearance of faint sounds (phase I), prolongation of the sounds into a murmur (phase II), increased intensity of the sounds (phase III) and muffling of the sounds (phase IV). Phase V refers to the complete disappearance of the sounds.

There is universal agreement that phase I is a relatively accurate index of systolic pressure. However, the index of diastolic pressure is controversial, with the conflict continuing to rest between muffling and complete cessation of the vascular sounds as the proper index. Available data indicate that in children muffling is probably the better criterion, but actually neither muffling nor cessation accurately reflects intraarterial pressure. Muffling gives readings that are too high and cessation gives readings that are too low.[10] The latest recommendations of the American Heart Association[4] regard muffling as the better index of diastolic pressure. However, a more recent report by the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure indicates that diastolic pressure should be equated with disappearance of sound.[11] Through the years, the position regarding the proper index

of diastolic pressure has vacillated and this has resulted in continued uncertainty regarding the index of choice. This is unfortunate because estimation of diastolic pressure is not uniformly employed and many of the "normal" diastolic values recorded in the literature have been obtained using different auscultatory criteria.

When there is a difference between muffling and cessation, both diastolic readings should be recorded. This permits subsequent identification of the criterion used. Also, the size of the cuff should be recorded. Both of these caveats are of particular importance in group practice or in a patient in hospital where serial blood pressures are often measured by different observers, and use of a different size cuff or a different index of diastolic pressure could lead to serious misinterpretations.

Some attention should be directed to the measurement of blood pressure in obese persons. It is particularly here that proper selection of cuff size is crucial, and, if one is to err, it is better to err on the side of too large a cuff. It is important to recognize that, although some of the cuff pressure may be dissipated in the excess fatty tissue, this is not necessarily the case.[12] In view of the higher incidence of hypertension in those who are obese, it is a mistake to dismiss an abnormally high reading simply on the basis of error due to cuff size.

Blood Pressure Measurements in Infants

Measurement of blood pressure in infants is unique and quite separate from measurement in older children. In infants, because of crying, movement and feeble vascular sounds, the auscultatory method for determining the level of arterial pressure is often inaccurate, difficult or even impossible. A wide variety of alternative methods have been described but of these, only the flush and the Doppler procedures have found widespread use.

The Flush Method

Historical aspects. The flush method of blood pressure measurement was introduced by Gaertner[13] in 1899, who used this procedure to measure the level of arterial pressure in the fingers. More than half a century later Cappe and Pallin[14] and Goldring and Wohltman[15] adopted his procedure for the determination of blood pressure in the hands and feet of infants.

Principle. The method is based on visualization and correlation with cuff pressure of flushing due to reentry of blood after the hand or foot is rendered bloodless. As described in the following section, this is accomplished by milking the blood from the hand or foot, applying an occluding pneumatic cuff to the wrist or ankle, and then reducing the cuff pressure to the point where arterial flow is resumed.

Technique. The procedure should be carried out in a well-lighted room with the infant in the supine position. Since activity and crying may profoundly affect the readings, it is important that the infant be as quiet and inactive as possible. If the baby cries during the procedure, it should be repeated. It may be necessary to have the baby suck on a pacifier or nipple even though the act of sucking may have a slight effect on the level of blood pressure.

Cuff selection need not be done with the same concern as for measurement by auscultation. Results of previous studies indicate that the width of the cuff may be as small as 5 cm or as great as 9.5 cm without any material effect on the readings obtained.[16,17]

The cuff is applied to the wrist for an upper extremity reading and to the ankle for a lower extremity reading. The hand or foot is then compressed by firmly wrapping it with a soft rubber drain or a rubber glove beginning at the tips of the digits and wrapping proximally to the lower edge of the cuff. To facilitate drainage, the extremity should be maintained at a level well above that of the heart. *Compression with one's hand is to be condemned* since it often produces inaccurate results because of incomplete drainage leading to poor definition of the end point.

Following completion of compression, the cuff is inflated to 200 mm of mercury, the elastic wrapping removed and the extremity is returned to heart level. The pressure within the cuff is gradually reduced until flushing of the balanced distal portion is observed. This is the end point (Figure 5). Although it was at first believed that the end point was a reflection of systolic pressure,[14,15,18] it has since been established that this is not the case. With a deflation rate not exceeding 5 mm of mercury per second, the manometer reading coinciding with the end point approximates the *mean* arterial pressure.[16,17,19(pp30-34)]

For the highest degree of accuracy it is essential that two observers participate in the procedure: one to deflate the cuff and read the manometer, the other to observe the flush and call out the end point. When used for diagnosis of coarctation of the aorta, three observers are required. In this situation, two cuffs (one for the wrist and one for

the ankle) are connected by a Y tube to a single manometer and by another Y tube to a single inflation bulb (Figure 6). The procedure is carried out as described above with the end points in the hand and foot being observed by two separate examiners. The procedure, originally described by Adams and co-workers[20] has the advantage of estimating the pressure gradient between the upper and lower extremities even if an infant is active or crying.

The advantages of the flush method are that it does not require the purchase of expensive equipment and can be carried out in a noisy environment. The disadvantages are that it cannot be done satisfactorily by a single examiner and that it does not measure systolic or diastolic pressures. At best it is only a *crude* indicator of mean pressure. Nevertheless, it is adequate for most clinical situations.

In using the flush method it is important to recognize that severe anemia, pronounced hypothermia or edema may affect the end point and cause gross inaccuracies.[21] Peripheral vascular stasis of the newborn and visible cyanosis due to congenital heart disease have no effect on the end point.[22]

The Doppler Method

Historical aspects. In 1957 Satomura[23] reported use of the Doppler principle for diagnosis of cardiovascular anomalies in human subjects. The principle was later adopted by Ware[24] for the indirect measurement of blood pressure. In 1967 it was found to correlate well with intraarterial measurements, and in 1968 the use of Doppler sphygmomanometry in infants was suggested by Stegall and colleagues.[25,26]

Principle. The instruments used for this method of blood pressure measurement are all based on the same principle as the transcutaneous ultrasonic blood-velocity meters used to measure blood flow. The system utilizes an ultrasonic beam generated by a piezoelectric crystal placed over the artery of an extremity. The beam is passed at an angle through the skin and underlying tissues to the arterial wall and is then reflected back to a second piezoelectric crystal. The frequency of the back-scattered sound is unchanged if there is no movement of the tissues. The relatively small motion of an uncompressed peripheral artery will not generate an audible signal. However, if a sphygmomanometer cuff is applied and inflated to a level between systolic and diastolic pressure, the artery will open and close with each cardiac cycle. The vessel wall movement will result in a change of frequency (Doppler shift) and the Doppler shift signals can be heard through headphones or a speaker system, seen on an oscilloscope or recorded as a written record. Some of the newer instruments are equipped with a continuous digital readout device. The Doppler shift signals differ from Korotkoff sounds in the following ways: (1) *Any* movement will generate the former, but vibratory motion in the *audible* range is required for the latter; (2) Doppler-shift signals are de-

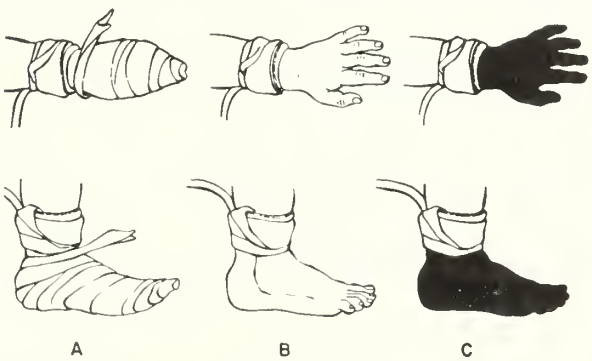


Figure 5.—Diagrams illustrating the technique of blood pressure measurement by the flush method. **A,** The cuff is applied to the wrist or ankle, and the distal portion of the extremity is wrapped snugly with an elastic bandage. **B,** The manometric pressure is then raised above the expected systolic pressure and the elastic wrapping removed. **C,** The blood pressure cuff is gradually deflated until the blanched portion flushes. This is read as the end point. (From Moss AJ, Adams FH: Problems of Blood Pressure in Childhood, 1962. Courtesy of Charles C Thomas, Publisher, Springfield, IL.)

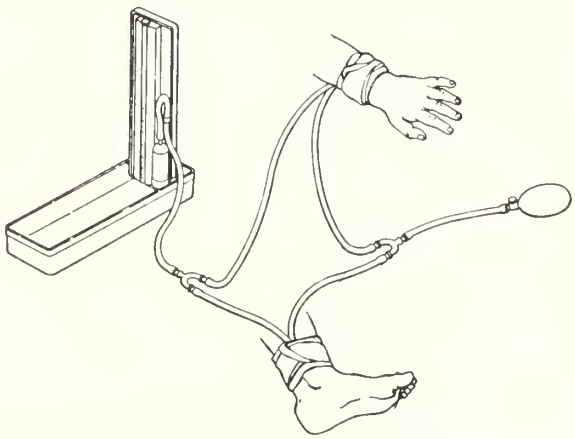


Figure 6.—Diagram showing the sphygmomanometer apparatus for simultaneous measurement of the flush blood pressure in the upper and lower extremities. The arrangement is of value in the diagnosis of coarctation of the aorta. (From Moss AJ, Adams FH: Problems of Blood Pressure in Childhood, 1962. Courtesy of Charles C Thomas, Publisher, Springfield, IL.)

tected during both opening and closure of the vessel whereas Korotkoff sounds are generated only during abrupt opening.[25]

Technique. The technique for measurement is quite similar to that used in the conventional auscultatory method. The artery is first located by palpation. The pneumatic cuff is then applied with the transducer positioned over the artery. The cuff is inflated well above the systolic arterial pressure and deflated at a rate of 3 to 5 mm of mercury per second. As long as the cuff pressure is greater than the intraarterial pressure, no Doppler shift signal will be detected. When the cuff pressure falls just below the intraarterial systolic pressure, Doppler shift signals will be generated by movement of the arterial wall and will appear and disappear in a manner similar to Korotkoff sounds. The onset of these signals is considered the index of systolic pressure. A change in character of the signal or complete disappearance is considered the index of diastolic pressure.

As with all other methods of measurement, every effort should be made to minimize anxiety and movement. A cuff of appropriate size must be used. As indicated previously, cuff widths of 5 to 9.5 cm do not introduce a significant error with the flush method. However, with the Doppler method, this is not the case.[27-29] A cuff that is too narrow will result in error on the high side. One that is too wide will result in error on the low side. As with auscultation, if one is to err it is probably best to err on the wide side.

The relationship of upper to lower extremity blood pressure using the Doppler method of measurement has not been firmly established. However, de Swiet and co-workers,[30] using the Doppler technique in newborn infants, found the systolic upper limb blood pressure to be greater than lower limb blood pressure. The mean difference was 17 mm of mercury.

Accuracy. There has been extensive experience with use of the Doppler method of blood pressure measurement under a wide variety of situations in neonates, infants and children.[27,28,31-47] A close agreement with intraarterial and auscultatory measurements has been shown.[25,27,31,33-36,41] In fact, there is some evidence to indicate that measurement of systolic pressure utilizing the Doppler technique more closely approximates intraarterial pressure than do measurements by auscultation of the Korotkoff sounds.[47] Estimation of diastolic pressure by the Doppler method apparently is not as reliable as estimation of the systolic pressure. Also, the reliability is to some extent dependent on the type of instrument used. In one recent study comparing different Doppler measuring devices to direct arterial pressure, it was found that no one device was completely accurate for *both* systole and diastole.[48]

The Doppler method is probably preferable to the flush method in that it requires only one examiner and registers with clinically acceptable accuracy both the systolic and diastolic pressures. However, a major disadvantage is the cost of the apparatus. Consequently it is being used chiefly in hospitals—in intensive care units, neonatal nurseries and operating rooms.

Normal Standards

Children and Adolescents

Unfortunately, it is difficult to reconcile the data of one study with those of others since the methods used have not been uniform. Variables include all aspects of measurement. In some studies the subjects rested before blood pressure measurement; in others they did not. Also, the position of the subject has not been uniform, the subjects being supine in some cases and seated in others. Some investigators recorded only a single measurement, others have averaged one measurement in each arm and still others have averaged two or more readings in the same arm. The effect of position on blood pressure has not been clearly delineated. In one study of normal men it was found that diastolic pressure was higher with the subjects standing.[49] Our own experience indicates that systolic pressure is somewhat higher in the right than in the left arm in normal persons (S. Londe, MD, and A. J. Moss, MD, unpublished data).

Some published standards of normal blood pressure have not taken sex and race into account. There is evidence to indicate that the level of blood pressure within certain age categories is not the same in boys and girls.[19(pp78-79),50,51] Also, there is evidence to suggest that the higher levels of blood pressure observed in black adults have their roots in childhood,[51-56] although there has not been total agreement on this point.[56-60]

The lack of consistency regarding measurement of diastolic pressure is another important variable which to this day has not been resolved. The American Heart Association has vacillated through the years from muffling of the vascular sounds—to disappearance—to muffling.[4,61,62] As indicated

previously, a more recent recommendation of still another national committee[11] has only added to the confusion.

Finally, even the type of instrument used to establish the normal range of blood pressure has not been consistent. Some of the values recorded in the literature have been obtained with use of a wide variety of automated and semiautomated devices. In a recent study of the performance of seven types of sphygmomanometers, it was found that the results varied widely when compared with intraarterial pressure.[63] One type of instrument overestimated systolic pressure by as much as 31 mm of mercury.

For all of these reasons, the limits of normal blood pressure still remain poorly defined in infants and children. *Severe* hypertension is clearly identifiable and usually presents no problem in deciding whether or not hypertension is present. *Mild* hypertension, however, is another issue. The discrepancies in some of the published data[50,...,64-66] have been dramatically illustrated by Voors and co-workers (Figure 7).[51]

From the foregoing, two caveats seem obvious. One is that if a clinician is to accept the normal standards of any given report, he *must* adhere to the methodology used in gathering the original data. Two is that "borderline hypertension" cannot be established on the basis of a single measurement. Repeated measurements over a period of time are required to obtain a trend.

Perhaps the most commonly used data are those derived from three separate studies and published by the National Heart, Lung and Blood Institute's task force (Figures 8 and 9).[67] In each instance the pressure measurement was done in the right arm within a few minutes of the child being seated. Muffling was used as the index of diastolic pressure. Values above the 95th percentile are considered elevated. It should be recognized, however, that even these carefully collected data have their shortcomings. In certain age categories, the values for both sexes were pooled. Also, the study groups consisted of some blacks as well as whites.

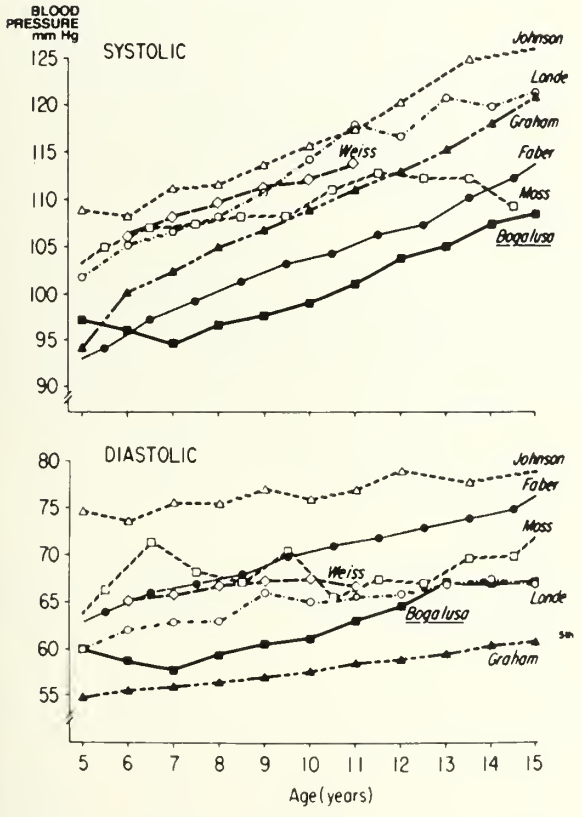


Figure 7.—Comparison of indirect blood pressure measurements of white school children, by age, among selected studies in the literature. Graham used the 5th Korotkoff phase for determining diastolic blood pressure. The other studies used either the 4th or a combination of 4th and 5th Korotkoff phases. (Reprinted by permission of authors and the American Heart Association, Inc., from Voors AW, et al.[51])

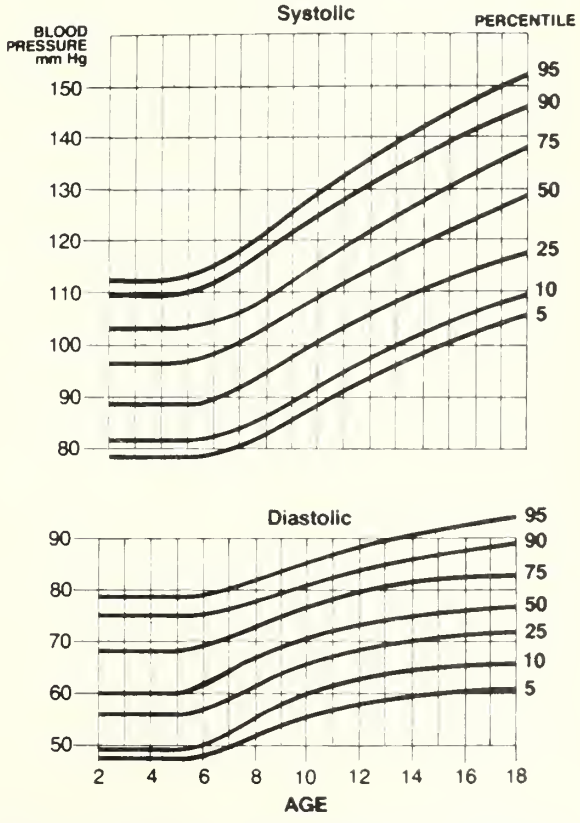


Figure 8.—Percentiles of blood pressure measurement in boys (right arm, seated). (Reproduced by permission from Blumenthal et al.[67])

The authors draw attention to the fact that "pressures obtained in a standardized fashion from a larger population base would be desirable."

From a purely practical standpoint, a systolic pressure of 140 mm of mercury in patients older than 10 years and 130 mm of mercury in children younger than 10 years might be considered as indicating hypertension. Likewise, a diastolic pressure of 90 mm and 85 mm of mercury in these respective age groups might also be indicative of hypertension.

Infants

Normal standards of blood pressure in infants are even more vague than in older children and adolescents. Fortunately, a *precise* definition is not crucial because hypotension or hypertension associated with conditions in this age group is usually so pronounced (that is, shock, renal disease, coarctation of aorta and the like) that there is little question regarding the significance of the reading.

Flush blood pressure values. Normal values during the first year of life were established by Moss and colleagues[68] and are shown in Table 1. The observed values did not exceed 100 mm of mercury in normal infants 1 to 12 months old. The average values in this age group were 72 mm of mercury for the wrist and 68 mm of mercury for the ankle.

Although Sullivan and Kobayashi[69] were unable to show by statistical methods a difference between hand and foot flush pressures, the general consensus is that a difference does indeed exist.[15,18,70] The extent and direction of this difference are of great importance when considering the diagnosis of coarctation of the aorta. Studies by Moss and associates[68] indicate that until 9 or 10 months of age, the flush pressure is higher in the hand than in the foot (Figure 10). Thereafter, the gradient reverses toward the adult pattern. The reasons for the reverse relationship between upper and lower extremity flush pressures in early infancy have not been clarified. In any event, it is suggested that a diagnosis of coarctation of the aorta during the early months of life should not be made on the basis of flush blood pressure values unless the gradient of simultaneously recorded pressures is greater than 20 mm of mercury.

Doppler blood pressure values. Definition of normal values in infants obtained by the Doppler method have become available only very recently.

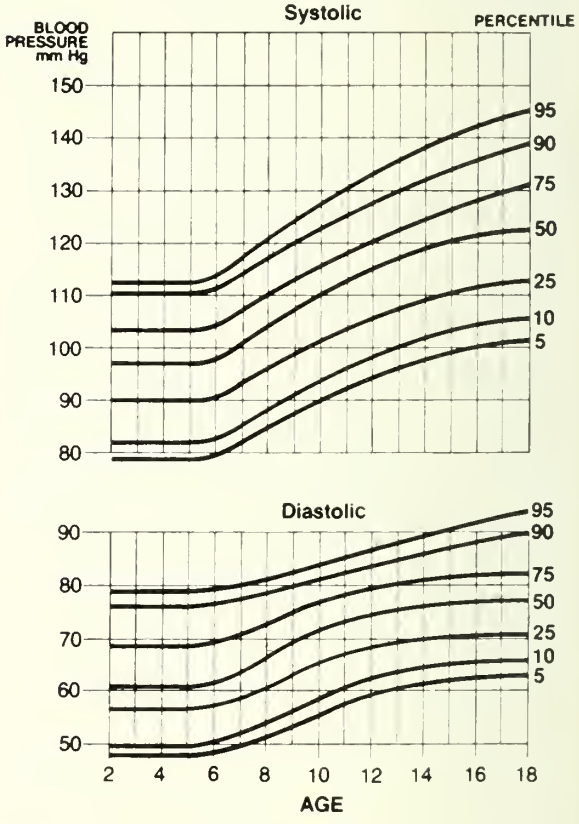


Figure 9.—Percentiles of blood pressure measurement in girls (right arm, seated). (Reproduced by permission from Blumenthal et al.[67])

TABLE 1.—*Arithmetic Mean Blood Pressure (mm of mercury) in the Various Age Categories With Observed Range of Values and Predicted Range of Normal Expressed as ±2 Standard Deviations**

Age	*No. of Subjects*	*Mean Blood Pressure at Wrist*	*Standard Deviation*	*Predicted Range of Values*	*Predicted Range of Values*	*Mean Blood Pressure at Ankle*	*Standard Deviation*	*Predicted Range of Values*	*Predicted Range of Values*
1-7 days	145	41	± 8.0	25-57	22-66	37	± 7.0	23-51	20-58
1-3 months . . .	155	67	±11.0	45-89	48-90	61	±10.5	40-82	38-96
4-6 months . . .	115	73	± 9.5	54-92	42-100	68	±10.0	48-88	40-104
7-9 months . . .	79	76	± 9.0	58-94	52-96	74	± 8.5	57-91	50-96
10-12 months . .	57	76	±14.0	62-90	62-94	79	± 8.5	62-96	56-102
1-12 months . .	406	72	±10.5	51-93	22-100	68	±12.0	44-92	20-104

*From Moss AJ, Adams FH: Problems of Blood Pressure in Childhood, 1962. Courtesy of Charles C Thomas, Publisher, Springfield, IL.

In a study of more than 3,000 awake infants by de Swiet and co-workers[71] the 95th percentile of systolic blood pressure was 113 mm of mercury between 6 weeks and 1 year of age (Table 2). With the current increased use of the Doppler method for measurement of blood pressure in infants, there will no doubt be additional information forthcoming relative to normal standards during the period of infancy.

Hypertension

Hypertension is known to be a common disorder in adults. The estimated prevalence in the United States is 10 percent to 20 percent[72-75] and may even be as high as 30 percent.[76] It is a serious disorder in that it is recognized as a precursor of stroke, coronary heart disease and renal insufficiency—each of which may result in premature death.[77] It is, in fact, one of the more common afflictions in America[78] and represents the basic underlying cause of a significant proportion of all cardiovascular deaths.

This situation does not exist in infants and children. Although of great importance in isolated cases, hypertension cannot be considered a common pediatric problem. Why, then, is it so important to routinely measure blood pressure in children and adolescents?

This is not a trivial question since it is conceivable that the current vigorous campaign to educate all physicians to record blood pressures in patients older than 2 or 3 years of age could have some undesirable side effects. Recognizing this, a committee sponsored by the American Heart Association[79] was careful to state:

> It is important to realize that even a one-time statement by a physician that a patient, whatever the patient's age may be, has "hypertension" can haunt a patient throughout a lifetime of job applications, life insurance rates, and social decisions such as choosing a vocation, deciding to marry, and determining when to seek advice for new signs and symptoms that may, or may not, be related to high blood pressure.

Perhaps the most outspoken opponent of the currently prevailing enthusiasm in support of routine measurement of blood pressure in children is North,[80] who estimates that such a program would result in raising the specter of "hypertension" in 4 million children with a high proportion being labeled as hypertensive. Moreover, he questions whether the potential benefit of such a program would justify a cost which he places at a minimum of $40 million.

Nevertheless, hypertension *is* encountered in children, although relatively infrequently. There

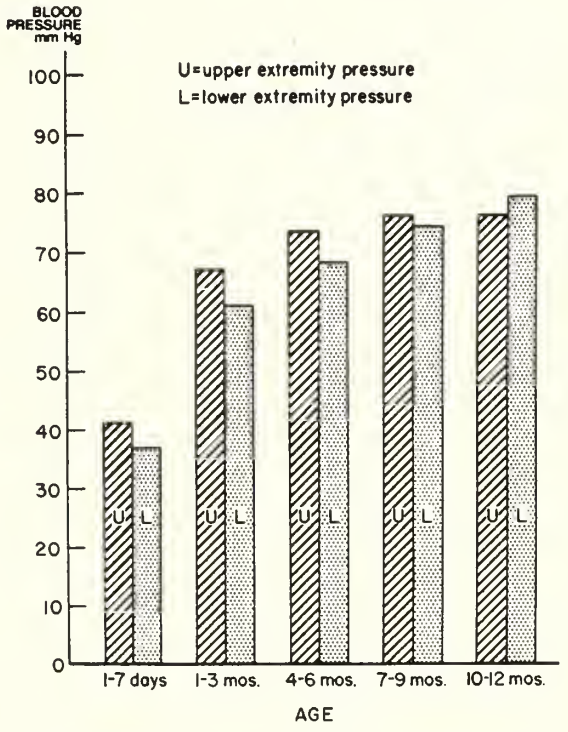


Figure 10.—Bar graph representing relationship of the arithmetic mean blood pressure and age in a cross-sectional study of 551 infants. (From Moss AJ, Adams FH: Problems of Blood Pressure in Childhood, 1962. Courtesy of Charles C Thomas, Publisher, Springfield, IL.)

TABLE 2.—*Means ± Standard Deviation of Blood Pressure (mm of mercury) by Sex at Ages 4 Days to 1 Year**

	Age					
	4 Days		*6 Weeks*			
	Awake	*Asleep*	*Awake*	*Asleep*	*6 Months†*	*1 Year†*
Boys	77±10 (92)‡	71±8 (809)	96±11 (594)	89±11 (260)	92±13 (457)	94±12 (695)
Girls	76±10 (82)	71±8 (757)	95±10 (537)	88±10 (246)	93±14 (401)	93±11 (643)

*Reproduced with permission from deSwiet et al[1]; Copyright, American Academy of Pediatrics, 1980.
†All infants were awake at ages 6 months and 1 year.
‡Number of infants is shown in parentheses.

is reason to believe that early recognition and treatment of primary hypertension may lead to a reduction in morbidity and mortality.[79,81] Current efforts directed toward the detection of hypertension in childhood seem to be justified and physicians should be urged to include measurement of blood pressure in the routine examination of children as young as 3 years of age.[67] Not only will this be helpful to children with unrecognized hypertension but could provide valuable information regarding the genesis and evaluation of primary hypertension in adults. There is no question that physicians who deal with children have, in the past, been remiss in recording blood pressure as so nicely shown by the studies of Pazdral and co-workers.[82]

Etiology

Most cases of hypertension in the pediatric age group are secondary to other causes. It has been estimated that 75 percent to 80 percent of diagnosed hypertension in prepubertal boys and girls is secondary to some underlying cause.[83] This is probably a conservative estimate. Considerable attention has been given in the literature to secondary hypertension so this will be touched on only briefly here.[84-95]

Secondary hypertension. The principal causes of secondary hypertension in childhood are renal disease and coarctation of the aorta, and only these will be considered. Of 563 young patients with secondary hypertension documented in the literature, 80 percent had renal disease and 2 percent had coarctation of the aorta.[90] Of the renal disorders, by far the most common is pyelonephritis. Other disorders include acute and chronic glomerulonephritis, congenital dysplastic kidney, polycystic kidneys, hydronephrosis and renovascular disease. Theories regarding the pathogenesis of hypertension secondary to chronic renal disease include (1) sodium retention with resultant hypervolemia, (2) inhibition of vasodilator substances secreted by the kidney (that is, prostaglandin A_2, killidin and bradykinin) and (3) elevated renin-angiotensin levels. The renin-angiotensin mechanism apparently operates as follows: decreased perfusion of the kidney (from whatever cause) stimulates release of renin which in turn results in an increase of angiotensin II. The latter causes peripheral vasoconstriction with increased resistance. Aldosterone production is also stimulated with resultant sodium retention, hypervolemia and increased cardiac output. Cardiac output may or may not fall to normal but the increased peripheral vascular resistance persists and this is reflected in a higher level of blood pressure.

Coarctation of the aorta has long been recognized as a cause of systemic hypertension. Regarding the mechanism of hypertension in this abnormality, the role of the kidneys versus the mechanical effects of the lesion itself has not been clearly defined. Observations by Harris and associates[96] indicate that mechanisms other than increased systemic resistance resulting from the coarctation are operative. These authors did not believe that renal ischemia was a factor. However, the early observations of Scott and Bahnson[97,98] in dogs with experimentally induced aortic coarctation make a compelling argument for a renal mechanism. These investigators found first of all that the carotid pressure rose progressively and did not reach a maximum until five to seven weeks after the operation. They reasoned that this would not be expected with a purely mechanical basis for the hypertension. Second, and more convincing, was their ingenious series of experiments that related the degree of hypertension to the anatomic level of the kidney. When the kidneys were left intact, hypertension occurred but when all functioning renal tissue was transplanted to an area above the experimental coarctation (to the carotid artery), the hypertension disappeared. This suggests a mechanism similar to the Goldblatt kidney in addition to the mechanical effect of the aortic stricture itself.

More recently, Alpert and co-workers[99] postulated that initially the aortic stricture causes a decrease in renal blood flow with resultant stimulation of the juxtaglomerular apparatus to secrete renin. As indicated previously, this causes an increased production of angiotensin and aldosterone, hormones that cause expansion of blood volume. The hypervolemia attempts to correct the decreased renal perfusion with feedback inhibition of the excessive renin secretion. They conducted experiments in human aortic coarctation and the results support their hypothesis. After administration of furosemide, plasma renin activity values were significantly higher in patients with coarctation of the aorta than in controls. Their data suggest that hypertension in coarctation of the aorta resembles a one-kidney Goldblatt model.

Primary hypertension. Primary hypertension is extremely rare in the prepubertal age group and far less common in adolescents than in adults. It

has attracted considerable attention in pediatrics because of the possibility that adult hypertension may first present in childhood as "borderline," "high normal," "unsustained" or "labile" hypertension. It has been suggested that *tracking* of blood pressure may exist and if this is the case, then early detection and management of hypertension would be a real possibility. Tracking is defined as the tendency for a blood pressure level at a given percentile to maintain that same percentile with continued growth and development. Studies by Zinner and co-workers[100] suggest that stratification of blood pressure begins and is detectable in childhood. However, subsequent longitudinal studies indicate that blood pressure does not track well and provide no evidence that casual blood pressure measurements in infancy or early childhood will enable identification of hypertensive adults with any degree of certainty.[101-103] Moreover, as indicated earlier, borderline hypertension has not yet been clearly defined. Adding to the confusion is the fact that the significance of labile hypertension and of systolic versus diastolic hypertension have not been clarified to everyone's satisfaction. In a recent publication, Kannel and associates[104] conclude that although it is unwise to label a patient as hypertensive on the basis of a single office blood pressure measurement, it is equally unwise to conclude that the patient who occasionally has a normal blood pressure level is not in jeopardy. Also, it is a mistake to dismiss as insignificant isolated systolic elevations.[104] There is evidence to indicate that systolic hypertension (in the absence of diastolic elevation) is associated with excess cardiovascular mortality in adults.[105] Finally, the methodology, muffling versus cessation of Korotkoff sounds, and the accuracy of indirect measurement of diastolic blood pressure remain open to question.

The cause of primary hypertension has not yet been established and controversy continues as to whether it is genetic or environmental. In a recent publication, Biron and Mongeau[106,107] review studies of adopted children and of stepchildren and conclude that genetic factors constitute the major component underlying the parent-sibling resemblance of blood pressure. Other studies support this view. Of particular interest is the work of Jones and Dowd[108] who were able to breed rats in which spontaneous genetic hypertension developed two days after birth. However, studies by Winkelstein and co-workers[109] strongly suggest that environmental factors play a significant role. These investigators showed spouse aggregation for couples married more than 15 years. Other studies have shown a familial influence on blood pressure which can be detected in children, suggesting that factors responsible for primary hypertension are *acquired* in childhood.[110] On the basis of available information, it is likely that persons are born with a genetic predisposition which then responds to environmental stimuli. A wide variety of environmental factors have been suggested. They will be considered only briefly here.

Salt. Salt has been implicated in the pathogenesis of hypertension.[111] It appears that hypertension for the most part is absent in primitive people and that blood pressure fails to rise with age as it does in civilized populations. This has been observed in many different areas of the world including New Guinea,[112] Malaysia,[113] the Easter Islands,[114] the Amazon Basin,[115] the San Blas Islands of Panama,[116] Uganda[117] and the Kalahari Desert in Africa.[118] Debilitation from disease does not appear to be predominantly responsible for the absence of hypertension in these populations because inhabitants of the Kalahari Desert[118] and of the Easter Islands[114] apparently were in good health. Nor can the lack of stress or the absence of obesity account for the absence of hypertension in unacculturated populations in that these are not consistent features.[111,119] Freis[111] deduces from these studies that the lack of salt in the diet is responsible for the low prevalence of hypertension in primitive populations.

The concept that a diet high in salt may cause hypertension is not without physiological basis. The ingestion of salt is known to increase extracellular fluid volume. The resulting increased venous return to the heart causes a rise in cardiac output. This in turn leads to autoregulation of the peripheral resistance vessels causing an increase in peripheal vascular resistance which in turn leads to elevation of systemic arterial pressure. However, as indicated in a recent publication by Dawber,[123] the hypothesis that a high sodium intake is linked to hypertension, though attractive, must still be considered unproved. In fact, Henry and Cassel[121] make a forceful argument against the hypothesis. They point out that blood pressure of Thai farmers is uniformly low despite a high salt intake and that there is much hypertension among the peasants of St. Kitts despite a much lower ingestion of salt.

Stress. Another factor long considered a possible cause of hypertension is stress. In an excellent

review, Henry and Cassel[121] present data supporting the concept that psychosocial stimulation may play an important role in the development of hypertension. These authors propose that environmental stimuli evoke emotional responses which interact with the vasomotor center of the cerebrum to produce increased peripheral vascular resistance mediated by way of the adrenergic system. The result is increased arterial pressure with no change in the extracellular fluid volume. The fact that psychotherapy may ameliorate hypertension is further evidence that stress may be a factor in the pathogenesis of hypertension.[122-125] Stone and De Leo[125] have provided biochemical evidence to indicate that the reduction of blood pressure induced by psychotherapy is associated with reduced peripheral adrenergic activity. However, Freis[111] cites studies that indicate competition, crowding, noise and other forms of socioeconomic stress are not directly correlated with hypertension.

Obesity. In both adults[126-128] and children,[129-131] obesity and hypertension have been positively correlated. Earlier impressions were that hypertension in obese persons is usually an artifact resulting from the subject's fat arm and the disproportionately narrow sphygmomanometer arm cuff but this cannot be assumed to be the case. Available evidence strongly suggests that obesity predisposes to the development or accentuation of hypertension.[132]

Pathophysiology

Blood pressure is affected by a complex mechanism consisting of many factors. These include chemical influences (angiotensin, prostaglandins, catecholamines, aldosterone, kallikreins), neural influences (sympathetic nervous system), cardiac output, elasticity of blood vessels and blood viscosity. Hypertension may result from alterations in any of these factors.[133-136] Stated otherwise, the *direct* determinants of blood pressure are (1) peripheral vascular resistance, (2) cardiac output, (3) aortic impedance and (4) diastolic arterial volume. *Indirect* determinants are (1) neural activity, (2) extracellular fluid volume (ECF), (3) renal pressor systems and (4) adrenal steroids.[87] Actually, from a purely hemodynamic standpoint, arterial hypertension is a result of increased cardiac output or increased systemic vascular resistance or both. Cardiac output is a function of stroke volume (the amount of blood ejected with each ventricular contraction) and heart rate. Stroke volume is determined in large measure by the amount of venous return (preload). Peripheral vascular resistance (afterload) is dependent primarily on the diameter of the arterioles, which may be altered functionally (contracted or relaxed) or anatomically as in atherosclerosis.

In primary hypertension, the two directly responsible hemodynamic determinants, cardiac output and peripheral vascular resistance, may be affected in a variety of ways. Salt and water retention due to whatever cause results in increased venous return to the heart which causes increased cardiac output which in turn causes an elevation in arterial pressure. Environmental factors such as stress or hormonal influences cause arteriolar constriction which leads to increased systemic vascular resistance which in turn provokes a rise in arterial pressure.

The relationship of the renin-angiotensin-aldosterone system to primary hypertension in adults has received considerable attention in the literature. Brunner and co-workers[137] classified adults with primary hypertension as having (1) high plasma renin, (2) normal plasma renin and (3) low plasma renin. These investigators presented data to suggest that patients with low renin hypertension had a better prognosis than those with high or normal renin hypertension. However, this apparently is not firmly established.[96] The relationship of plasma renin to the pathogenesis and prognosis of primary hypertension in children and adolescents has not yet been clearly defined and further work is needed in this area.

Management

The first step in the management of hypertension is its recognition. Greatly elevated levels of blood pressure are immediately identified as abnormal and the diagnosis of hypertension is readily apparent. Borderline or labile hypertension is quite another matter and here the diagnosis of hypertension or even the potential for hypertension should be made with deliberation and with caution. A casual remark, unless carefully worded, can have a devastating impact on an adolescent and the parents. This can not only cause anxiety but can affect a number of important decisions as indicated previously. Moreover, such things as restriction of diet and regulation of activity are not well received by adolescents. In doubtful cases, blood pressure should be measured serially at 6- to 12-month intervals. It goes without saying that a complete physical examination should be made

to rule out underlying disorders that may cause hypertension. Obese persons in any event should be encouraged to lose weight. A careful family history is essential and hypertension in the immediate family should be viewed as a *red flag* which mitigates against dismissal of a single high reading as unequivocally insignificant. This recommendation is made despite one study of a small group of offspring of hypertensive parents which did not show there to be hypertension in an age period up to 22 years.[138]

If mild hypertension is found to exist on three or four occasions, an analysis of urine should be done. Other diagnostic studies depend upon the patient's course. At some point, in cases of persistent mild hypertension, serum electrolytes, blood urea nitrogen, serum creatinine, uric acid and serum glucose determinations may be done, as well as an x-ray study of the chest, an electrocardiogram and a rapid sequence intravenous pyelogram. In my experience, these additional studies have not proved helpful.

With hypertension of moderate or severe degree, the patient should be referred to an appropriate specialist.

Diet. Available evidence suggests that in cases of established primary hypertension, limitation of salt intake, reduction of weight if obese and a structured exercise program are indicated. Moreover, agents known to cause or aggravate hypertension such as licorice, orally taken contraceptives, corticosteroids or sympathomimetic drugs should be avoided.[136]

Exercise. Exercise is believed to have a beneficial effect on hypertension. The question frequently arises, however, concerning the advisability of participation in sports. Riopel and associates[139] provided reference values of blood pressure in normal children during treadmill exercise. These investigators observed that in some normotensive adolescents, the systolic pressure approached 200 mm of mercury whereas the diastolic pressure either diminished or remained essentially unchanged. Nudel and co-workers[140] found the blood pressure responses to be the same in labile hypertensive adolescents as in normotensives during maximal exercise testing. However, in adolescents with *sustained* primary hypertension, systolic pressure rose to as much at 240 mm of mercury.

Strong[141] finds no evidence for increased morbidity or mortality in adolescents who participate in sports if the resting arterial pressure does not exceed 170 mm of mercury systolic or 100 mm diastolic and believes such persons should be cleared for participation. He states that competitive athletics should probably be forbidden to adolescents with more severe hypertension. The American Academy of Pediatrics Committee on Pediatric Aspects of Physical Fitness, Recreation and Sports[142] does not recommend limitation of sports participation for adolescents with blood pressure not exceeding 160 mm of mercury systolic and 95 mm diastolic. The committee considers these values to represent *mild* hypertension. Participation in competitive athletics in cases of secondary hypertension should be determined on the basis of the underlying disorder. The level of systolic blood pressure with intense exercise that would constitute a definite contraindication to strenuous competition is not established, but the committee suggests that it is in the range of 230 to 250 mm of mercury. Finally, the committee concludes that even with mild hypertension such exercise as weight lifting should not be permitted. There appears to be a consensus that in adolescents with hypertension evaluation by exercise testing should be done before judgment is made regarding their participation in strenuous competitive sports.[139-142]

Drugs. Institution of antihypertensive drug therapy is a decision that should not be taken lightly. The problem of drug compliance in children and adolescents is a real one.[143] Also to be considered, of course, is the incidence of adverse effects. Chasis[144] maintains that the value of antihypertensive drug therapy for the general hypertensive population has not yet been established. Freis[145] bitterly contests this. Most authorities agree that at least in cases of severe hypertension, drug therapy is warranted. Whether it is justified in cases of moderate hypertension in children and adolescents remains an open question but it would not seem indicated when hypertension is mild.

Specific drug therapy will be discussed only briefly here. For a more detailed discussion, the reader is referred elsewhere.[87,132,136,137,146-149]

Hypertension secondary to renal disease not infrequently reaches alarmingly high levels and requires urgent treatment. In such cases, sodium nitroprusside or diazoxide are the drugs of choice because of their prompt action. These agents act directly on the peripheral vascular smooth muscle causing vasodilatation and a reduction in systemic vascular resistance.

Long-term antihypertensive drug therapy is not

commonly employed in the pediatric age group for the following reasons: (1) persistent hypertension is relatively uncommon, (2) the level of hypertension is often not of sufficient magnitude to require drug therapy and (3) the effects of antihypertensive drugs on growing children have not yet been clearly delineated. However, there are situations in which long-term drug therapy is necessary, such as when persistent severe hypertension is present in children and possibly when moderate hypertension is (if one assumes moderate hypertension to be levels above 160 mm of mercury systolic and 95 mm diastolic).

Three types of drugs may be used (Table 3). These include diuretics, adrenergic antagonists and peripheral vasodilators. It is customary to start with only one drug and to add others as needed. Which drug is used initially and which should be added subsequently is a matter of some controversy. It is my preference to begin with a diuretic and if the desired response is not obtained, to add an adrenergic blocking agent. If the response is still inadequate, then a peripheral vasodilator is added.

Diuretics. Not only do diuretics promote urinary excretion but they also reduce extracellular volume and thus intravascular volume. The reduced venous return to the heart is reflected in a fall of blood pressure. However, because of autoregulation of cardiac output resulting in increased systemic vascular resistance, the fall in blood pressure may be only slight. Of the diuretics, chlorothiazide is the one most commonly used. Furosemide and ethacrynic acid are more potent diuretic agents but both have undesirable side effects. Spironolactone is a much less potent diuretic and is not commonly used in the treatment of hypertension, except perhaps in combination with another diuretic to counteract potassium loss.

β-Adrenergic blocking agents. These agents act directly on the β-receptors in the heart causing a decrease in heart rate and in cardiac contractility, thus leading to reduced cardiac output. The reduction in cardiac output is reflected by a fall in

TABLE 3.—*Drugs for Use in Treatment of Hypertension*

Specific Drugs	*Daily Dose (mg/kg)*	*Adverse Reactions*
Diuretic agents		
Chlorothiazide	10-20	Hyperglycemia, hyperuricemia, weakness, restlessness, vertigo, dizziness, nausea, vomiting, diarrhea, hematologic
Hydrochlorothiazide	1-2	Same as above
Furosemide	0.5-1	Hearing impairment, tinnitus, nausea, vomiting, diarrhea, hematologic
Ethacrynic acid	0.5-1	Same as above
Spironolactone	1-2	Gynecomastia, diarrhea, drowsiness, headache, dermatitis, mental confusion, irregular menses
Agents acting on adrenergic nervous system		
Propranolol	0.5-1	Bradycardia, heart failure, mental depression, weakness, fatigue, bronchospasm, diarrhea, vomiting, hematologic
Methyldopa	10-40	Sedation, asthenia, headache, dizziness, bradycardia, edema, nausea, vomiting, myalgia, lupus-like syndrome, jaundice, pancreatitis
Guanethidine	0.2-0.5	Dizziness, lassitude, syncope, paresthesias, encephalopathy, hepatitis, nausea, vomiting, dermatitis, hematologic
Reserpine	0.02-7	Sedation, nasal congestion, dryness of mouth, mental depression, arrhythmias, nausea, vomiting, diarrhea, hematologic
Vasodilators		
Hydralazine	1	Headache, palpitations, anorexia, nausea, vomiting, diarrhea, tachycardia, angina pectoris, nasal congestion, flushing, depression, arthralgia, splenomegaly, hepatitis, lymphadenopathy, hematologic
Diazoxide*	5 μg/kg by rapid infusion	Sodium and water retention, hyperglycemia, myocardial ischemia, cerebral ischemia
Sodium nitroprusside*	50 mg/liter of 5 percent dextrose in water: 0.01-0.16 ml/kg/minute	Nausea, headache, dizziness, abdominal pain

*For treatment of hypertensive crises.

blood pressure. These agents also block receptors in the central nervous system with resulting peripheral vasodilatation which may further augment the antihypertensive effect. The drug commonly used in children for this purpose is propranolol.

α-Adrenergic blocking agents. These agents or drugs that inhibit or prevent the release of norepinephrine from the sympathetic nerve endings are rarely used in children. These drugs cause a fall in blood pressure by virtue of their effect on the peripheral vascular smooth muscle with a resultant decrease in systemic vascular resistance. α-Adrenergic blocking agents include reserpine, guanethidine, methyldopa and clonidine. Of these, only methyldopa is used to any extent in children, but because of its untoward side effects, it is usually reserved for cases in which other combinations of drugs fail.

Vasodilators. Vasodilators act directly on the peripheral vasculature causing dilatation with a decrease in peripheral vascular resistance. Hydralazine is the most popular vasodilator for use in the pediatric age group.

A method commonly employed in the drug management of hypertension in children and adolescents is to treat initially with chlorothiazide and then, if necessary, to add propranolol. If this combination is ineffective, hydralazine may be added as a third drug. The bradycardic effect of propranolol tends to offset the tachycardic effect of hydralazine.

Finally, much has been made in the literature of the value of renin profiling in selection of antihypertensive drugs for adults. For example, it is known that diuretics increase plasma renin activity and β-adrenergic blocking agents decrease activity. In children, however, age related changes in plasma renin levels are not yet known so the value of renin profiling in the pediatric age group has not been established.

Conclusions and Recommendations

- Whether muffling or cessation of the vascular sounds is the better index of diastolic pressure has not been established. Most pediatricians use muffling but both values should be recorded.
- Two or three measurements should be taken and all should be recorded.
- A single, modestly high reading is indication for serial measurements in 6 to 12 months.
- If the blood pressure is high while seated, measurements should be recorded with the patient in the supine position and vice versa.
- For all practical purposes, a blood pressure of 140 mm of mercury systolic or 90 mm diastolic in patients older than 10 years of age should be considered as indicative of hypertension; a systolic pressure of 130 mm of mercury or a diastolic pressure of 85 mm in children younger than 10 should be considered as indicative of hypertension. These are purely arbitrary values.
- If one is to use published standards of normal as a reference, strict adherence to the same methodology used in the published study is essential.
- The upper limit of normal for blood pressure in infants aged 1 to 12 months is 100 mm of mercury by the flush method and 113 mm of mercury by the Doppler method.
- The presence of hypertension requires a thorough history and physical examination. If hypertension is sustained, selected laboratory studies are indicated.
- Patients with mild, labile or borderline hypertension should have serial measurements of blood pressure before a definitive diagnosis is made.
- Adolescents with hypertension may participate in strenuous physical activity and competitive sports if the resting systolic pressure does not exceed 160 mm of mercury and the diastolic pressure does not exceed 95 mm of mercury.
- Antihypertensive drug therapy is indicated in cases of severe hypertension. It is not indicated for *mild* hypertension. However, in selected cases of *moderate* hypertension (family history of early cardiovascular disease or hypertension, progressive rise in serial readings), antihypertensive drug therapy may be indicated.

Addendum

To add to the existing confusion regarding diastolic pressure determination by auscultation, the American Heart Association committee[150] recently issued the following statements: "The onset of muffling is the fourth phase and should be regarded as the best index of diastolic pressure for children. The fifth phase occurs when sounds become inaudible and should be regarded as the best index of diastolic blood pressure in adults."

REFERENCES

1. Halliburton WD: Traube waves and Mayer waves. Q J Exp Physiol 122:227-229, 1920

2. Moss AJ, Adams FH: Auscultatory and intra-arterial pressure: A comparison in children with special reference to cuff width. J Pediatr 66:1094-1097, 1965

3. Steinfeld L, Alexander H, Cohen ML: Updating sphygmomanometry. Am J Cardiol 33:107-110, 1974

4. Kirkendall WM, Burton AC, Epstein FH, et al: Recommendations for human blood pressure determination by sphygmomanometers. Circulation 36:980-988, 1967

5. Burch GE, Shewwy L: Sphygmomanometric cuff size and blood pressure recordings. JAMA 255:1215-1218, 1973

6. Park MK, Guntheroth WC: Direct blood pressure measurements in brachial and femoral arteries in children. Circulation 41: 231-237, 1970

7. Pascarelli EF, Bertrand CA: Comparison of blood pressures in the arms and legs. N Engl J Med 270:693-698, 1964

8. Nielsen PE, Oxenboll B, Astvad K, et al: Auscultatory measurement of blood pressure performed by the doctor on duty. Acta Med Scand 198:35-37, 1975

9. Ragan C, Bordley J III: Accuracy of clinical measurements of blood pressure with note on auscultatory gap. Bull John Hopkins Hosp 69:504-528

10. Moss AJ, Adams FH: Index of indirect estimation of diastolic blood pressure—Muffling versus complete cessation of vascular sounds. Am J Dis Child 106:364-367, 1963

11. Moser M (Chairman): Report of the Joint National Committee on detection, evaluation, and treatment of high blood pressure—A cooperative study. JAMA 237:255-261, Jan 17, 1977

12. Karvonen MJ, Telivo LJ, Jarvinen EJK: Sphygmomanometer cuff size and the accuracy of indirect measurement of blood pressure. Am J Cardiol 13:688, 1964

13. Gaertner G: Ueber-einen neuen Blutdruckmesser (tonometer). Wien Klin Wchnsche 12:696-698, 1899

14. Cappe BE, Pallin IM: Systolic blood pressure determination in the newborn and infant. Anesthesiology 13:648-650, 1952

15. Goldring D, Wohltmann H: Flush method for blood pressure determinations in newborn infants. J Pediatr 40:285-289, 1952

16. Moss AJ, Liebling W, Austin WO, et al: An evaluation of the flush method for determining blood pressure in infants. Pediatrics 20:53-62, 1957

17. Moss AJ, Liebling W, Austin WO, et al: Determining blood pressure in infants—Use of the flush technique. Calif Med 87:166-167, 1957

18. Reinhold J, Pym M: Determination of blood pressure in infants by flush method. Arch Dis Child 30:127-129, 1955

19. Moss AJ, Adams FH: Problems of Blood Pressure in Childhood. Springfield, IL, Charles C Thomas, 1962

20. Adams PM, Keele M, Baronofsky I: Coarctation of the aorta in infants, *In* Essays on Pediatrics in Honor in Irvine McQuarrie. Minneapolis, Lancet Publications, 1955, p 25

21. Virnig NL, Reynold JW: Reliability of flush blood pressure measurements in the sick newborn infant. J Pediatr 84:594-598, 1974

22. Moss AJ, Adams FH: Flush blood pressure and intra-arterial pressure—A comparison of methods in infants. Am J Dis Child 107:489-491, 1964

23. Satomura S: Ultrasonic Doppler method for the inspection of cardiac functions. J Acoust Soc Am 29:1181-1185, 1957

24. Ware RW: New approaches to the indirect measurement of human blood pressure. Third Nat Biomed Sci Instr Symp (ISA), 1965, BM-65

25. Stegall HF, Kardon MB, Kemmerer WT: Indirect measurement of arterial blood pressure by Doppler ultrasonic sphygmomanometry. J Appl Physiol 25:793-798, 1968

26. Stegall HF, Rushmer RF, Baker DW: A transcutaneous ultrasonic blood-velocity meter. J Appl Physiol 21:707-711, 1966

27. Black IFS, Kotrapu N, Massie H: Application of Doppler ultrasound to blood pressure measurement in small infants. J Pediatr 81:932-935, 1972

28. Hill GE, Machin RH: Doppler determined blood pressure recordings—The effect of varying cuff sizes in children. Anesth Soc J 23:323-326, 1976

29. Park MK, Kawabori I, Guntheroth WG: Need for an improved standard for blood pressure cuff size. Clin Pediatr 15:784-787, 1976

30. de Swiet M, Peto J, Shinebourne EA: Difference between upper and lower limb blood pressure in normal neonates using Doppler technique. Arch Dis Child 49:734-735, 1974

31. Kemmerer WT, Ware RW, Stegall HF, et al: Blood pressure measurement by Doppler ultrasonic detection of arterial wall motion. Surg Gynecol Obstet 131:1141-1147, 1970

32. Janis KM, Kemmerer WT, Kirby RR: Intraoperative Doppler blood pressure measurements in infants. Anesthesiology 33:361-363, 1970

33. Zahed B, Sadove MS, Hatano S, et al: Comparison of automated Doppler ultrasound and Korotkoff measurements of blood pressure of children. Anesth Analg 50:699-704, 1971

34. Janis KM, Kemmerer WT, Hagood CO Jr: Doppler blood pressure measurements in infants and small children. J Pediatr Surg 6:70-72, 1971

35. Hernandez A, Goldring D, Hartmann AF Jr: Measurement of blood pressure in infants and children by the Doppler technique. Pediatrics 48:788-794, 1971

36. Kirkland RT, Kirkland JL: Systolic blood pressure measurement in the newborn infant with the transcutaneous Doppler method. Pediatrics 80:52-56, 1972

37. Waltemath CI, Preuss DD: Assessment of cardiovascular function during operation using Doppler technic. Am Surg 38: 352-354, 1972

38. Lang VD, Keller F, Kolodziejzak F, et al: Indirect determination of systolic and diastolic blood pressure values in premature infants, newborn infants and infants using the electrooscillography and Doppler's ultrasonic technics (comparative study). Monatsschr Kinderheilkd 121:131-134, 1973

39. Gordon LS, Johnson PE, Penido JRF, et al: Systolic and diastolic blood pressure measurements by transcutaneous Doppler ultrasound in premature infants in critical care nurseries and at closed-heart surgery. Anesth Analg 53:914-918, 1974

40. Rashmi A, Guha DK, Jain KK, et al: Indirect blood pressure measurement by Doppler in the newborns. Indian Pediatr 11: 729-733, 1974

41. Whyte RK, Elseed AM, Fraser CB, et al: Assessment of Doppler ultrasound to measure systolic and diastolic blood pressures in infants and young children. Arch Dis Child 50:542-544, 1975

42. de Swiet M, Francourt R, Peto J: Systolic blood pressure variation during the first 6 days of life. Clin Sci Mol Med 49: 557-561, 1975

43. de Swiet M, Fayers P, Shinebourne EA: Blood pressure survey in a population of newborn infants. Br Med J 2:9-11, 1976

44. Fuchshofen M, Metze H: Blood pressure of premature infants within the first 3 weeks of life. Monatssch Kinderheilkd 124: 596-598, 1976

45. Pipkin FB, Phil D, Smales ORC: A study of factors affecting blood pressure and angiotensin II in newborn infants. J Pediatr 91:113-119, 1977

46. Kuzemko JA, Hircock S, Fisher S, et al: Measurement of systolic blood pressure in the preterm baby by the transcutaneous Doppler method. Arch Dis Child 52:413-414, 1977

47. Steinfeld L, Dimich I, Reder R, et al: Sphygmomanometry in the pediatric patient. J Pediatr 92:934-938, 1978

48. Reder RF, Dimich I, Cohen ML: Evaluating indirect blood pressure measurement techniques: A comparison of three systems in infants and children. Pediatrics 62:326-330, 1978

49. Tuckman J, Shillingford J: Effect of different degrees of tilt on cardiac output, heart rate, and blood pressure in normal man. Br Heart J 28:32-39, 1966

50. Londe S: Blood pressure in children as determined under office conditions. Clin Pediatr 5:71-78, 1966

51. Voors AW, Foster TA, Frerichs, et al: Studies of blood pressures in children, ages 5-14 years, in a total biracial community—The Bogalusa heart study. Circulation 54:319-327, 1976

52. Comstock GW: An epidemiologic study of blood pressure levels in a biracial community in the southern United States. Am J Hyg 65:271-315, 1957

53. Langford HG, Watson RL, Douglas BH: Factors affecting blood pressure in population groups. Trans Assoc Am Physicians 81:135-146, 1968

54. Weiss NS, Hamill PVV, Drizd T: Blood pressure levels of children 6-11 years: Relationship to age, sex, race and socioeconomic status, DHEW Pub No (HRA) 74-1617. US Department of Health, Education and Welfare, 1973, pp 1-20

55. Kotchen JM, Kotchen TA, Schwertman NC, et al: Blood pressure distributions of urban adolescents. Am J Epidemiol 99: 315-324, 1974

56. Reichman LB, Cooper BM, Blumenthal S, et al: Hypertension testing among high school students—I. Surveillance procedures and results. J Chronic Dis 28:161-171, 1975

57. Johnson BC, Remington RD: A sampling study of blood pressure levels in white and Negro residents of Nassau, Bahamas. J Chronic Dis 13:39-51, 1961

58. Rose G: A study of blood pressure among Negro schoolchildren. J Chronic Dis 15:373-380, 1962

59. Kilcoyne MM, Richter RW, Alsup PA: Adolescent hypertension—I. Detection and prevalence. Circulation 50:758-764, 1974

60. Londe S, Gollub SW, Goldring D: Blood pressure in black and in white children. J Pediatr 90:93-95, 1978

61. Bordley J III, Connor CAR, Hamilton WF, et al: Recommendations for human blood pressure determinations by sphygmomanometers. Circulation 4:503-509, 1951

62. Committee of the American Heart Association: Recommendations for human blood pressure determinations by sphygmomanometers. JAMA 147:632-636, 1951

63. Hunyor SN, Flynn JM, Cochineas C: Comparison of performance of various sphygmomanometers with intra-arterial blood pressure readings. Br Med J 2:159-162, 1978

64. Faber HK, James CA: The range and distribution of blood pressures in normal children—Clinical application of statistical methods to the interpretation of deviation from the normal average. Am J Dis Child 22:7-28, 1921

65. Graham AW, Hines EA, Gage RP: Blood pressures in children between the ages of five and sixteen years. Am J Dis Child 69:203-214, 1945

66. Johnson BC, Epstein FH, Kjelsberg MO: Distributions and familial studies of blood pressure and serum cholesterol levels in a total community, Tecumseh, Michigan. J Chronic Dis 18:147-160, 1965

67. Report of Task Force on Blood Pressure Control in Children: Prepared by the National Heart, Lung and Blood Institute's task force on blood pressure control in children. Pediatrics 59: 797-820, May 1977

68. Moss AJ, Liebling W, Adams FH: The flush method for determining blood pressures in infants—II. Normal values during the first year of life. Pediatrics 21:950-957, 1958

69. Sullivan MP, Kobayashi M: Evaluation of the flush technique for the determination of blood pressure in infancy. Pediatrics 15:84-87, 1955

70. Forfar JO, Kibel MA: Blood pressure in the newborn estimated by the flush method. Arch Dis Child 31:126-130, 1956

71. de Swiet M, Fayers P, Shinebourne EA: Systolic blood pressure in a population of infants in the first year of life: The Brompton study. Pediatrics 65:1028-1035, 1980

72. Moss A, Scott G: Hypertension: United States, 1974—Advance data No 2. US Department of Health, Education and Welfare, Public Health Service, Health Resources Administration, Nov 8, 1976

73. Krovetz LJ: Blood pressure. J Pediatr 87:1013-1014, 1975

74. Tobian LJ Jr: The clinical approach to essential hypertension. Hosp Practice, Jul, 33-44, 1975

75. Wilber JA, Barrow JG: Hypertension—A community problem. Am J Med 52:653-663, 1972

76. Voors AW, Webber LS, Berenson GS: Epidemiology of essential hypertension in youth—Implications for clinical practice. Pediatr Clin N Am 25:15-27, 1978

77. Veterans Administration Cooperative Study Group on Antihypertensive Agents: Effects of treatment on morbidity of hypertension—Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. JAMA 202:1028-1034, 1967

78. Kannel WB, Castelli WP, McNamara PM, et al: Role of blood pressure in the development of congestive heart failure: The Framingham study. N Engl J Med 287:781-787, 1972

79. American Heart Association: Committee on Arteriosclerosis and Hypertension in Childhood of the Council on Cardiovascular Disease in the Young. Pediatrics 56:3-5, 1975

80. North AF Jr: Is it worth $50 million. Pediatrics 59:788-789, 1977

81. Veterans Administration Cooperative Study Group on Antihypertensive Agents: Effects of treatment on morbidity in hypertension: III. Influence of age, diastolic pressure, and prior cardiovascular disease: Further analysis of side effects. Circulation 45:991-1004, 1972

82. Pazdral PT, Lieberman HM, Pazdral WE, et al: Awareness of pediatric hypertension—Measuring blood pressure. JAMA 235: 2320-2322, 1976

83. Lieberman E: Children Have Hypertension Too!—A Handbook for Pediatric Hypertension. American Heart Association, Los Angeles, 1979, p 2

84. Freis ED: Office evaluation of the hypertensive patient. Mod Concepts Cardiovasc Dis 32:817-820, 1963

85. Rance CP, Arbus GS, Balfe JW, et al: Persistent systemic hypertension in infants and children. Pediatr Clin N Am 21:801-824, Nov 1974

86. Loggie JMH: Hypertension in children and adolescents. Hosp Pract, 81-92, Jun 1975

87. Dustan HP: Evaluation and therapy of hypertension—1976. Mod Concepts Cardiovasc Dis 45:97-104, 1976

88. Londe S, Goldring D: High blood pressure in children: Problems and guidelines for evaluation and treatment. Am J Cardiol 37:650-657, 1976

89. Loggie JMH: Systemic hypertension, *In* Moss AJ, Adams FH, Emmanouilides GS (Eds): Heart Disease in Infants, Children and Adolescents. Baltimore, Williams & Wilkins, 1977, pp 645-659

90. Londe S: Causes of hypertension in the young. Pediatr Clin N Am 25:55-66, 1978

91. New MI, Levine LS: Adrenocortical hypertension. Pediatr Clin N Am 25:67-82, 1978

92. Robson AM: Special diagnostic studies for the detection of renal and renovascular forms of hypertension. Pediatr Clin N Am 25:83-98, 1978

93. Loggie JMH: Juvenile hypertension, *In* Moss AJ (Ed): Pediatrics Update: Reviews for Physicians. New York, Elsevier, 1979, pp 237-250

94. Loggie JMH, New MI, Robson AM: Hypertension in the pediatric patient: A reappraisal. J Pediatr 94:685-699, 1979

95. Turner MC, et al: Blood pressure elevation in children with orthopedic immobilization. J Pediatr 96:989-992, 1979

96. Harris JS, Sealy WC, DeMaria W: Hypertension and renal dynamics in aortic coarctation. Am J Med 9:734-746, 1950

97. Scott HW Jr, Bahnson HT: Evidence for renal factor in hypertension of experimental coarctation of aorta. Surgery 30:206-217, 1951

98. Scott HW Jr, Collins HA, Langa AM, et al: Additional observations concerning the physiology of the hypertension associated with experimental coarctation of the aorta. Surgery 36:445-459, 1954

99. Alpert BS, Bain HH, Balfe JW, et al: Role of the renin-angiotensin-aldosterone system in hypertensive children with coarctation of the aorta. Am J Cardiol 43:828-834, 1979

100. Zinner SH, Martin LF, Sacks F, et al: A longitudinal study of blood pressure in childhood. Am J Epidemiol 100:437-442, Dec 1974

101. Rosner B, Hennekens CH, Kass EH, et al: Age-specific correlation analysis of longitudinal blood pressure data. Am J Epidemiol 106:306-313, Oct 1977

102. Clarke WR, Schrott HG, Leaverton PE, et al: Tracking of blood lipids and blood pressures in school age children: The Muscatine study. Circulation 58:626-634, Oct 1978

103. Levine RS, et al: Tracking correlations of blood pressure levels in infancy. Pediatrics 61:121-125, 1978

104. Kannel WB, Sorlie P, Gordon T: Labile hypertension: A faulty concept—The Framingham study. Circulation 61:1183-1187, 1980

105. Kannel WB, Dawber TR, McGee DL: Perspectives on systolic hypertension—The Framingham study. Circulation 61:1179-1182, 1980

106. Biron P, Mongeau J: Familial aggregation of blood pressure and its components. Pediatr Clin N Am 25:29-33, 1978

107. Biron P, Mongeau J, Bertrand D: Familial aggregation of blood pressure in adopted and natural children, *In* Oglesby P (Ed): Epidemiology and Control of Hypertension. Miami, Symposium Specialists, 1975, pp 397-405

108. Jones DR, Dowd DA: Development of elevated blood pressure in young genetically hypertensive rats. Life Sciences 9:247-250, 1970

109. Winkelstein W Jr, Karzon DT, Rush D, et al: Familial aggregation of blood pressure—Preliminary report. JAMA 195:848-850, Mar 7, 1966

110. Zinner SH, Levy PS, Kass EH: Familial aggregation of blood pressure in childhood. N Engl J Med 284:401-404, 1971

111. Freis ED: Salt, volume and the prevention of hypertension. Circulation 53:589-595, 1976

112. Maddocks I: Blood pressure in Melanesians. Med J Aust 1:1123-1126, 1967

113. Burns-Cox CJ, MacLean JD: Splenomegaly and blood pressure in an Orang Asli community in West Malaysia. Am Heart J 80:718-719, 1970

114. Cruz-Coke R, Etcheverry R, Nagel R: Influence of migration on blood pressure of Easter Islanders. Lancet 1:697-699, 1964

115. Lowenstein FW: Blood pressure in relation to age and sex in the tropics and subtropics—A review of the literature and an investigation in two tribes of Brazil Indians. Lancet 1:389-392, 1961

116. Kean BH: The blood pressure of the Cuna Indans. Am J Trop Med 24:341-343, 1944

117. Shaper AG: Cardiovascular disease in the tropics—III. Blood pressure and hypertension. Br Med J 3:805-807, 1972

118. Kaminer B, Lutz WPW: Blood pressure in Bushmen of the Kalahari Desert. Circulation 22:289-295, 1960

119. Page LB, Damon A, Moellering RC Jr: Antecedents of cardiovascular disease in six Solomon Islands societies. Circulation 49:1132-1146, 1974

120. Dawber TR: Annual discourse—Unproved hypothesis. N Engl J Med 9:452-458, 1978

121. Henry JP, Cassel JC: Psychosocial factors in essential hypertension—Recent epidemiologic and animal experimental evidence. Am J Epidem 90:171-200, 1969

122. Benson H, Rosner BA, Marzetta BR, et al: Decreased bloodpressure in pharmacologically treated hypertensive patients who regularly elicited the relaxation response. Lancet 1:289-291, Feb 23, 1974

123. Kristt DA, Engel BT: Learned control of blood pressure in patients with high blood pressure. Circulation 51:370-278, 1975

124. Patel C, North WRS: Randomized controlled trial of yoga and biofeedback in management of hypertension. Lancet 2:93-95, 1975

125. Stone RA, DeLeo J: Psychotherapeutic control of hypertension. N Engl J Med 294:80-84, 1976

126. Levy RL, et al: Overweight: Its prognostic significance in relationship to height and cardiovascular-renal diseases. JAMA 131:951-953, 1946

127. Oberman A, Lane NE, Harlan WR, et al: Trends in systolic blood pressure in the thousand aviator cohort over a twenty-four-year period. Circulation 36:812-822, Dec 1967

128. Stamler J: Epidemiology of coronary heart disease. Med Clin North Am 57:5-46, 1973

129. Johnson AL, Cornoni JC, Cassel JC, et al: The influence of race, sex and weight on blood pressure behavior in young adults. Am J Cardiol 35:523-530, Apr 1975

130. Rames LK, Clarke WR, Connor WE, et al: Normal blood pressures and the evaluation of sustained blood pressure elevation in childhood: The Muscatine study. Pediatrics 61:245-251, Feb 1978

131. Goldring D, Londe S, Sivakoff M, et al: Blood pressure in a high school population—I. Standards for blood pressure and the relation of age, sex, weight, height, and race to blood pressure in children 14 to 18 years of age. J Pediatr 91:884-889, Dec 1977

132. Lieberman E: Essential hypertension in children and youth: A pediatric perspective. J Pediatr 85:1-11, 1974

133. Page IH: Pathogenesis of arterial hypertension. JAMA 140:451-458, 1949

134. Page IH: Arterial hypertension in retrospect. Circ Res 34:133-142, 1974

135. Hmer LB, Gruskin AB: The physiology of blood pressure regulation—Normal and abnormal. Pediatr Ann 6:373-383, 1977

136. Bailie MD, Mattioli LF: Hypertension: Relationships between pathophysiology and therapy. J Pediatr 96:789-797, 1980

137. Brunner HR, Laragh JH, Baer L, et al: Essential hypertension: Renin and aldosterone, heart attack and stroke. N Engl J Med 286:441-449, Mar 2, 1972

138. Kaplan BS, Fox H, Seidman E, et al: Normal blood pressure in offspring of persons with essential hypertension. Can Med Assoc J 118:1415-1417, Jun 10, 1978

139. Riopel DA, Taylor AB, Hohn AR: Blood pressure, heart rate, pressure-rate product and electrocardiographic changes in healthy children during treadmill exercise. Am J Cardiol 44:697-704, 1979

140. Nudel DB, et al: Exercise performance of hypertensive adolescents. Pediatrics 65:1073-1078, 1980

141. Strong WB: Hypertension and sports. Pediatrics 64:693-695, 1979

142. Thorton ML, et al: Cardiac evaluation for participation in sports. Am Acad Pediatr Policy Statement, Apr 1977

143. Ruley EJ: Compliance of young hypertensive patients. Pediatr Clin N Am 25:175-182, 1978

144. Chasis H: Appraisal of antihypertensive drug therapy. Circulation 50:4-8, 1974

145. Freis ED: Rebuttal: Appraisal of antihypertensive drug therapy. Circulation 50:9-10, 1974

146. Freis ED: Medical treatment of chronic hypertension. Mod Concepts Cardiovasc Dis 40:17-22, 1971

147. Finnerty FA: Drugs used in the treatment of hypertension. Mod Concepts Cardiovasc Dis 42:33-36, 1973

148. Finnerty FA: Critical considerations in the treatment of arterial hypertension. Mod Concepts Cardiovasc Dis 42:37-40, 1973

149. Sinaiko AR, Mirkin BL: Clinical pharmacology of antihypertensive drugs in children. Pediatr Clin N Am 25:137-159, 1978

150. Kirkendall WM, et al: American Heart Association—Recommendations for human blood pressure determinations by sphygmomanometers. Circulation 62:1145A-1155A, 1980

Toxoplasma Gondii Transmission From Cats to Children

RECOMMENDATIONS to avoid *Toxoplasma gondii* transmission: one is that cats should not be fed raw meat. And if they are, because they hunt, they are likely to shed infectious feces at some time. Pregnant women should avoid cats and especially should not change a cat's litter box. It takes about two to three days at room temperature for the oocyst feces to become infected. Therefore, cat litter should be changed every day. It should not be randomly dumped outdoors, but it can be sterilized either by boiling or with dry heat or by burning. (I have never known a cat owner, however, who boiled or burned cat litter.) It could be flushed down the toilet, if you can stand the plumbing bills. Ordinary household disinfectants do not dependably kill oocysts. And if you do like to eat raw or undercooked meat, it should be solidly frozen before being prepared for a meal.

—PHILIP J. GOSCIENSKI, MD, *San Diego*

Extracted from *Audio-Digest Pediatrics,* Vol. 26, No. 23, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1577 East Chevy Chase Drive, Glendale, CA 91206.

Specialty Conference

Refer to: Harker LA, Thompson AR, Harlan JM: Thrombosis: Its role and prevention in cardiovascular events—Part II. —Hematology-Oncology Conference, University of Washington (Specialty Conference). West J Med 134:315-332, Apr 1981

Participants
LAURENCE A. HARKER, MD
ARTHUR R. THOMPSON, MD, PhD
JOHN M. HARLAN, MD

An edited transcription of a Hematology-Oncology Conference, Division of Hematology, University of Washington School of Medicine, Seattle.

Thrombosis: Its Role and Prevention in Cardiovascular Events—Part II

Anticoagulants and Thrombolytic Agents in Cardiovascular Disease

ARTHUR R. THOMPSON, MD, PhD*

ANTICOAGULANT THERAPY with heparin followed by warfarin is a well-established regimen for limiting deep venous thrombi or pulmonary emboli. In the past, it has also been popular to anticoagulate patients with myocardial infarction to prevent further thrombus formation. Over the past two decades many studies have been reported that assess the effect of anticoagulants on reinfarction or mortality. More recently, the use of low doses of heparin has been evaluated in the prevention of venous thromboembolism in patients during hospital stays for myocardial infarction. Experimental trials of acute thrombolytic therapy with urokinase or streptokinase infusion have also been done in patients with myocardial infarction to determine if these agents improve survival or reduce infarct size by lysis of a preformed thrombus. A final group of cardiac disorders are those in which orally given anticoagulants have been used to reduce the risk of arterial embolization from mural thrombi secondary to transmural infarction, atrial arrhythmias, a large left atrium or prosthetic heart valves. Before summarizing the results of clinical trials, structural and functional aspects of the specific anticoagulants and plasminogen activators will be discussed.

Therapeutic Agents and Their Modes of Action

Heparin is a sulfonated mucopolysaccharide composed of repeating disaccharide units which are most commonly iduronic acid and N-acetylglucosamine. Two to three sulfate groups are present per disaccharide unit and at the reducing end of the molecule, galactose and xylose residues are attached to one of several seryl side chains which are found in specific intracellular binding proteins in vivo. It should be noted that heparin molecules are "polydisperse" with a molecular weight range of 6,000 to 14,000. A specific tetrasaccharide sequence (Figure 2A) with two nonsulfonated uronic acid residues appears to be responsible for the anticoagulant activity.[81] Active fractions which bind to antithrombin may be of higher or lower molecular weight, depending on whether they have one or two tetrasaccharide sequences. These specific sequences bind to charged amino groups of certain lysyl residues on antithrombin III, which enhances the reactivity of a specific arginyl group (Figure 2B).[82] The latter positively charged side chain binds to the negatively charged binding pocket of active serine proteases (for example, thrombin, factors IXa, Xa, XIa and VIIa, and plasmin) to form a stable enzyme-

*Associate Professor of Medicine, Division of Hematology, University of Washington, and with the U.S. Public Health Service Hospital and the Puget Sound Blood Center.

Part II of a two-part Specialty Conference. Part I appeared in the March issue.

Reprint requests to: Laurence A. Harker, MD, Division of Hematology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104.

ABBREVIATIONS USED IN TEXT

BMH = Bronx Municipal Hospital (study)
CAD = coronary artery disease
MI = myocardial infarction
MRC = Medical Research Council (study)
VAH = Veterans Administration Hospitals (study)

inhibitor complex. Heparin may also interact with the enzyme directly (for example, thrombin or factor IXa),[83] independently modulating the reactivity of the protease with antithrombin III (Figure 2C).

Anticoagulant-active fractions represent a variable but relatively small portion of commercial preparations. Organ or species of origin or the preparative process itself may produce heparins of different specific activities, although the commonly available types from porcine intestine or bovine lung are as effective, therapeutically, as any other. Doses are standarized for anticoagulant effect—that is, units as opposed to weight—by clotting screening tests. It is possible that certain side effects and, of major importance, thrombocytopenia, may be caused by fractions with relatively little anticoagulant effect,[73] which is a strong argument for having more purified preparations available.

Physiologically, heparin immediately inhibits clotting screening tests. The thrombin time (when its control is greater than 18 seconds) is the most sensitive test as it is remarkably prolonged at even 0.01 units per ml. Tests of intrinsic clotting such as partial thromboplastin or recalcification times are of intermediate sensitivity, which makes them ideal for monitoring the therapeutic effect as they are essentially doubled by 0.2 to 0.5 units per ml of heparin. The extrinsic tests such as the prothrombin time are only slightly prolonged by even 0.5 units per ml.

Concerning the rationale advanced for low-dose heparin, the fact that heparin-antithrombin III is such a *universal* inhibitor of clotting proteases suggests that earlier stages, before amplified prothrombin conversion, are more sensitive to this inhibition. However, without additional knowledge of the relative rates of the enzymatic steps or their normal or pathologic initiation steps, a potential pharmacological effect of heparin administered in low doses can only be speculated on from the mechanistic standpoint. Although in the test tube, factor Xa formation is more sensitive to smaller amounts of heparin than is thrombin, the rele-

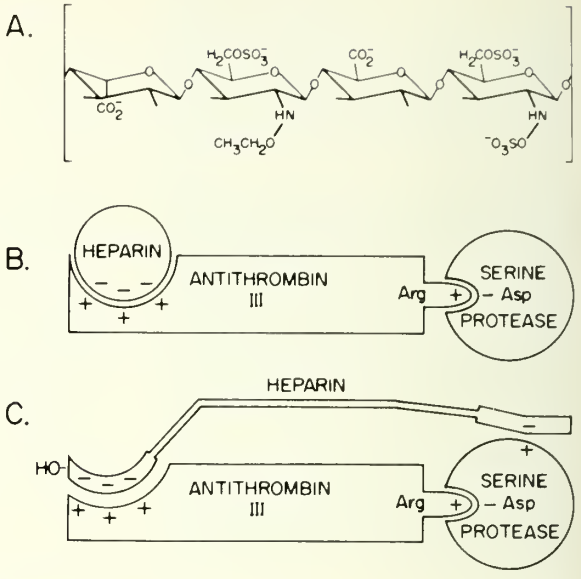


Figure 2.—Heparin. **A**, Structure of the active tetrasaccharide. **B and C**, Proposed mechanisms for the interaction of heparin with antithrombin III to facilitate inhibition of active clotting factors, the serine proteases of blood.

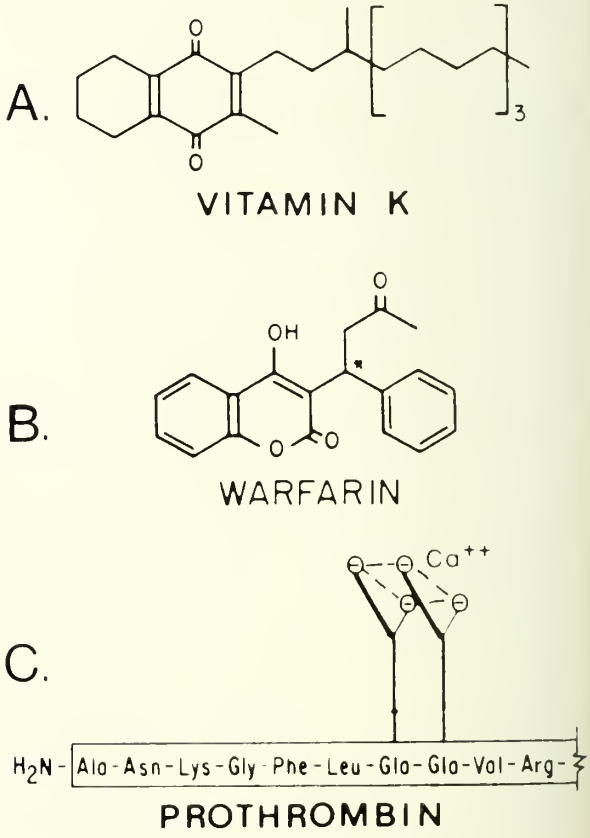


Figure 3.—**A and B**, Structure of vitamin K and warfarin. **C**, Adjacent γ-carboxyglutamyl residues at positions 7 and 8 of prothrombin, forming one of the tight calcium-binding sites.

vance of this inhibition remains to be assessed in more complicated physiological systems and, eventually, in vivo.

Warfarin. The coumarin nucleus is similar chemically to the naphthoquinone derivative, vitamin K (Figure 3A and 3B), and indirect evidence has strongly suggested interaction at a common receptor site. Once a vitamin K-dependent protein is synthesized in the liver, specific glutamyl residues are carboxylated in a post-protein synthesis reaction. Sterically adjacent dicarboxylic residues (Gla's) form a negative charge density which serves as a tight calcium binding site as illustrated in Figure 3C.[84] This allows the trace plasma protein clotting factors to bind to phospholipid surfaces and to achieve a sufficient local concentration to be activated and in turn to interact with their substrates. With vitamin K antagonism, as by warfarin, the carboxylation is incomplete and abnormal proteins then circulate with impaired clotting activity.[85,86]

The physiological effect of warfarin as an anticoagulant is based upon the activities of the four vitamin K-dependent clotting factors, namely prothrombin and factors VII, IX and X. Since these four have different half-lives, with factor VII being the shortest, it is possible to prolong the prothrombin time within 24 hours or less after a single large dose of warfarin without having reduced the other factors to levels which would limit hemostasis.

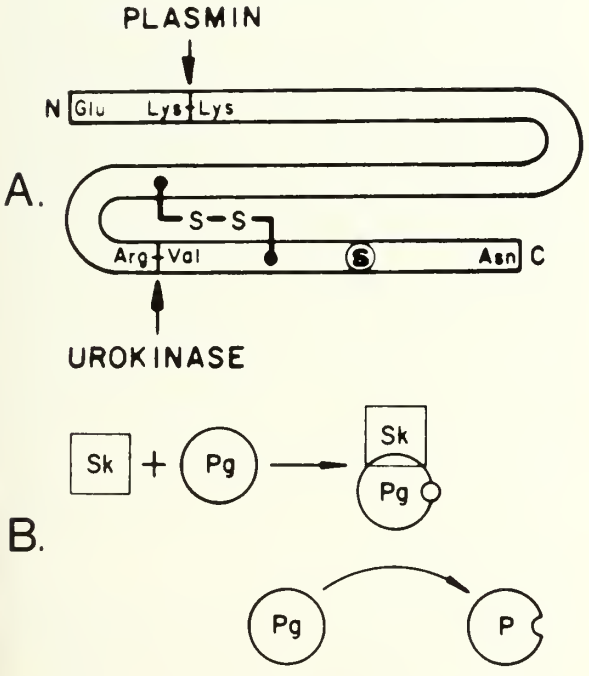


Figure 4.—A, Structure of plasminogen with activation (Arg-Val) and secondary (Lys-Lys) cleavage sites. Plasmin consists of Glu- or Lys- forms with an aminoterminal heavy chain disulfide-linked (S-S) to the carboxy terminal light chain; the latter contains its active center Ser (S). **B,** Stoichiometric interaction of streptokinase (Sk) with plasminogen (Pg) to form a complex capable of converting other molecules of plasminogen to plasmin (P).

Thrombolytic agents. These drugs function as activators of plasminogen, which is then capable of cleaving several bonds of fibrin to solubilize fibrin clots. An additional effect of plasmin is its ability to inactivate intermediate cofactors in the steps of the clotting scheme (for example, factors V and VIII) which produce anticoagulant effects. The specific activators include urokinase and streptokinase.[87] Urokinase is a protease found in trace amounts in normal urine and is immunologically identical with a tissue-derived enzyme that is presumably its in vivo correlate. Figure 4A shows the structure of plasminogen and its urokinase cleavage site which converts the plasminogen to an active serine protease. Streptokinase is a nonenzymatic exoprotein from group C beta-hemolytic streptococci and acts by forming a stoichiometric complex with plasminogen, which allows its active site to become exposed, generating plasmin from other plasminogen molecules (Figure 4B). Note that there is no difference in therapeutic effects between the two agents except that antigenicity may limit the use of the bacterial protein.

After infusion of thrombolytic agents, it is necessary to generate sufficient amounts of plasmin to overcome the potent α-2 antiplasmin inhibitor.[88] As free plasmin can not only digest fibrin and clots but also destroy circulating fibrinogen and factors V and VIII, serious hemostatic defects are readily achieved such that the therapeutic index is extremely narrow. Patients receiving these drugs must be monitored carefully and contraindications include recent operation, cardiopulmonary resuscitation, stroke, atrial fibrillation or any additional hemostatic defect.[89] These exclusions eliminate many patients being considered as candidates for thrombolytic therapy, complicating its clinical assessment.

Anticoagulant Therapy in Myocardial Infarction

Effects on Mortality and Reinfarction

Of the plethora of studies on the use of anticoagulants in myocardial infarctions over the past

two decades, three large-scale, controlled trials of full-dose anticoagulation have been reported. These include the Medical Research Council (MRC),[39] and Bronx Municipal Hospital (BMH)[90] studies that assessed patients in the early to middle 1960's and the Veterans Administration Hospitals' (VAH)[40] study conducted half a decade later. The MRC and VAH studies were multicenter trials of some 10 to 12 rather homogeneous institutions; the BMH study used a single hospital with entries over a six-year period (1961 to 1967). Entry criteria for the VAH study were the most restrictive as patients with shock, pulmonary edema or intractable arrhythmias were not included; furthermore, it was designed to restrict the sample to male patients younger than 75 years of age.

Patients with a high probability of myocardial infarction were selected for each trial and 8 percent of the analyzed MRC cases, on retrospective analysis, could not be diagnosed as probable or definite. The 17 patients (less than 2 percent) without substantiated diagnosis in the VAH trial were excluded from analysis. The BMH study did not specify the number of patients without a definite diagnosis although in 61 percent of their patients diagnostic electrocradiographic changes occurred. The BMH study was further confounded by the following factors: (1) twice as many cases were assigned to treatment as to control groups, (2) the percentage of controls increased during the last three years of the trial, (3) "periodic checks" suggested that nearly a third of the patients with myocardial infarction admitted to their hospital during the six years were not included and (4) after analyzing the data through the fourth year (in which it was concluded that women did benefit from anticoagulants) the 30 women studied during the fifth year were all treated and not included in the series.

Anticoagulant regimens were comparable using 36 or more hours of full-dose heparinization during which time orally given agents were administered; heparin was then discontinued only after a test of extrinsic clotting activity was significantly prolonged. In all three studies an attempt was made to *blind* patients with respect to placebo, although it was admitted by the BMH trial that physicians' "placebo compliance" was difficult to obtain.

The findings on mortality and reinfarction are summarized in Table 1. The percent mortality over 28 days was comparable for placebo and anticoagulated groups in the MRC and VAH studies and for males in the BMH study. The higher mortality (31 percent) among control females in the BMH study was an effect largely confined to older women and led to the above-mentioned modification of their protocol. Percent of reinfarctions was not significantly different from controls except for the women in the BMH study. In the MRC series, however, women were not significantly different from men. The overall lower values for treatment and control groups noted in the VAH study presumably reflect their entry restrictions and, perhaps, the fact that the study was conducted in a later period. Thus, with the possible exception of older women, patients with acute myocardial infarction had no reduction in mortality or reinfarction during the first 28 days when full-dose anticoagulation therapy was carried out.

Since these trials appeared, three additional large scale studies have emerged. These were retrospective, epidemiologic studies from Israel[91] and Maryland,[92,93] and it was reported that patients treated with anticoagulants had a two- to threefold lower inhospital mortality than those who were not. The amount, dosage and duration of treatments were neither specified nor compared and patients were entered into the studies in the mid-1960's. An exception to the latter was in the

TABLE 1.—*Mortality and Reinfarction Findings From Three Large-scale, Controlled Trials of Full-Dose Anticoagulation*

Study	*N*	*Accession Time**		*Percent Mortality (28 days)*		*Percent Reinfarction (28 days)*	
		<24 h	*<72 h*	*Control*	*Treated*	*Control*	*Treated*
MRC[39]	1,427	44	82	18	16	8.4	6.5
BMH†[90]	1,136	100	..	..	..	..	..
males	745	..	..	15	16	10.0	11.0
females	391	..	..	31	15	19.0	13.0
VAH[40]	999	52	100	11	10	4.8	3.4

MRC = Medical Research Council BMH = Bronx Municipal Hospital VAH = Veterans Administration Hospitals

*MRC and VAH studies were reported as time after symptoms; BMH, after admission; numbers represent percent accessed.
†BMH male and female data are presented separately as analyzed by authors (see text).

second study from Baltimore,[93] in which a comparable cohort was also collected in 1971 for comparison. In these three series, untreated groups were somewhat smaller and, although comparable by clinical characteristics, they were not matched. The frequency of treatment varied among hospitals surveyed and, presumably, among different physicians at given hospitals as the decision to treat had been entirely at their discretion. One study[92] compared treatment within coronary care units, which also showed increased hospital survival for anticoagulated patients; the percentage of patients receiving additional care and given anticoagulants, however, was higher. Considering the inhospital or short-term data, the 31 percent nontreated fatality rates as compared with the 18 percent treated fatality rates (the somewhat lower values from the Israel study reflect the 21 days used as a cutoff) are of interest in that they were comparable to the nontreated results from the previous randomly controlled studies. There is no question that prospective randomization is by far a more valid study procedure. Indeed, in a similar retrospective study[94] significant differences disappeared when the severity of mycoardial infarction was statistically controlled, demonstrating a selection bias.

Interest in anticoagulant therapy was renewed when Chalmers and co-workers[95] summarized results from all previous studies. These workers noted that when the percentages of controlled studies (including large- and small-scale series) were pooled, the small, nonsignificant differences noted in mortality became significant by simple chi-square (x^2) analysis. The problems of combining data from studies collected over a 10 to 15 year period (particularly in an area evolving rapidly such as the medical management of myocardial infarction) must be considered. The scientific validity of pooling and the fact that exact numbers rather than percentages should be pooled are additional points that have been soundly challenged in the critique by Goldman and Feinstein.[96]

In addition to these major design criticisms, it should be noted that the value of a large N (number in the population under study), statistically, is to assure that a given sample is representative. Analyses, particularly using the simple x^2 statistic, are affected by N such that with a large sample, the P value (level of significance) needs to be evaluated in conjunction with a measure of association.* It is possible to have a highly significant but nonethless trival relationship. Unfortunately, this latter criticism can be applied to all of the studies of anticoagulants in myocardial infarction.

Use of multivariate analysis, for example, not just to compare treatment and control groups, but for weighting the separate variables, is a powerful means to control for the net effect of several small differences between predictors which might erroneously suggest a significant difference in a more simple analysis. This point is underscored by a recent simulated random trial by Lee and associates[97] in which 1,073 medically treated patients with coronary artery disease were randomly allocated to two groups. A subgroup of nearly 400 patients (with three vessel disease and an abnormal left ventricular contraction pattern) showed significantly different survivals between the randomly divided groups. By univariate analysis, eight variables were identified as significant predictors of survival. However, controlling by a multivariate approach, the predictive contribution of six of these variables was not significant; significance was reduced in the remaining two. Consequently, disregard of the joint effects of multiple variables in analysis can lead to spurious effects even in groups that appear to be matched.

Concerning long-term anticoagulation after myocardial infarction, it appears that one is only exposing patients to the risks of bleeding without providing any benefit.[98] Although follow-up survivals from one retrospective study showed continued improvement in patients who received some therapy while in hospital,[93] this was not supported in the data available from the men in the random, prospective BMH study.[99] Indeed, the very premise that led to trials of anticoagulants is, in retrospect, fallacious: clotting factors are clearly less important than the vessel wall and platelets in arterial thrombogenesis.

Before searching further for a role of anticoagulant therapy in myocardial infarction, it is essential to delineate what aspects of the disease process might be amenable to intervention. One is left, then, with the risks of venous thromboembolism and arterial emboli secondary to mural thrombi. It is important to keep the relative fre-

*When used for analyzing ordinal data, x^2 is less powerful than other nonparametric statistics, such as rank order measurements, because it disregards ordinality. Moreover, the dichotomous dependent variable, death, when treated as interval data, is amenable to regression analysis, which would allow much more powerful statistics to be used.

quency of these complications in perspective, particularly as they relate to other variables, such as ambulation and exercise, and to other changing aspects of management. Furthermore, as uncommon events, statistical assessment of the preventive value of anticoagulants, for example, is encumbered by major sampling considerations.[100]

Anticoagulants for Thromboembolic Complications

Basic concepts of and the reliability of diagnostic criteria for pulmonary embolism have been shaped by large scale trials of fibrinolytic agents in the early 1970's.[101] Although studies in the 1960's, for example, looked at the frequency of thromboembolism with or without anticoagulants, the fact that clinical measurements were as often right as wrong for deep leg vein thrombi or emboli to the lungs make these aspects of the studies uninterpretable. Perfusion lung scanning data were not introduced until the VAH study.[40] Whereas newer methodology such as calf scanning using labeled fibrinogen offers greater objectivity, the prevalence of positive results makes extrapolation to the less frequent occurrence of a pulmonary embolism difficult, since it is at best a crude indicator of a tendency that in an occasional person may be ominous.

The frequencies of embolic and bleeding complications from the three randomized studies (Table 1) are summarized in Table 2. This section will confine itself to venous involvement where all studies, with the exception of findings for males in the BMH series, found significant reductions. As mentioned above, however, only the VAH study relied upon confirmation of pulmonary embolism with lung scans; these represented nearly all of the events they listed and included 11 probable and 13 certain cases among the control group (4.8 percent) and 11 probable and 1 certain case in the treated group (2.4 percent). Although this difference is significant (x^2 equals 4.17, P is less than 0.05) the strength of the relationship is weak (ϕ, as a measure of association, equals 0.06). The variable degree of mobilization was an additional feature that needs to be considered in comparing these studies. In the MRC series, for example, most patients were not sitting out of bed until after the 21st day in hospital, whereas in the BMH study earlier ambulation was stressed such that most patients were walking by the end of the first week. In the most relevant information from the VAH study, it was mentioned that more than 91 percent of surviving patients had remained in hospital as of the 27th day.

Because of interest about venous thromboembolism in surgical patients, calf scanning using fibrinogen labeled with iodine 125 was done to assess the status of patients admitted to coronary care units.[102-104] The latter two of the retrospective studies suggested that in patients after anticoagulation there were fewer positive scans. Controlled but small trials with full doses of heparin[105,106] reported that the nearly 30 percent incidence of positive scans among control patients was reduced in the patients receiving anticoagulants.

Again, as a sequel to the experience in surgical patients, low doses of heparin were used after an acute myocardial infarction and results from five randomized studies[107-111] are summarized in Table 3. Three of these, including the two more recent ones, showed significant decreases. There were differences in methodology including the criteria for positivity or the treatment schedule; of note, the two negative studies used the greater amounts of heparin. Of relevance is the identification of other factors which profoundly influence the positivity of calf scanning data.[111-113] Smoking, which actually decreases the percent of positive scans,

TABLE 2.—*Complications of Acute Myocardial Infarction and Therapy From Three Large-scale, Controlled Trials*

Study	N	Percent Venous Thromboembolism*		Percent Arterial Emboli†		Percent Bleeding‡	
		Control	Treated	Control	Treated	Control	Treated
MRC§[39]	1,427	9.8	3.8	3.4	1.3	0.8	3.5
BMH[90]	1,136	..	..	..	..	..	..
males	745	1.5	1.8	1.5	1.8	6.9	13.5
females	391	3.9	1.5	3.9	1.5	1.6	11.8
VAH[40]	999	3.5	1.4	5.6	0.8	1.2	2.6

MRC = Medical Research Council BMH = Bronx Municipal Hospital VAH = Veterans Administration Hospitals

*Pulmonary emboli (for VAH, includes certain or probable by lung scan) and thrombophlebitis.
†BMH study reported only cerebrovascular accidents.
‡Major bleeding except BMH study where presumably minor blood losses were included (although 20 percent of their treated group had therapy discontinued for bleeding).
§MRC reported number of incidents, not patients, of a given complication; the percentage as patients involved was slightly lower.

TABLE 3.—*Randomized Trials of Low-Dose Heparin in Acute Myocardial Infarction*

Reference	Fibrinogen ^{125}I Calf Scans N-positive/N-tested (Percent Positive)* Control	Treated†
A. Handley[107]	7/24 (29)	6/26 (26)
B. Gallus et al[108]	1/13 (8)	1/14 (7)
C. Warlow et al[109]	11/64 (17)	2/63 (3)
D. Emerson & Marks[110]	14/41 (34)	2/37 (5)
E. Pitt et al[111]	11/37 (30)	5/36 (14)
no CHF	6/30 (20)	4/27 (15)
with CHF	5/7 (71)	1/9 (11)

CHF = congestive heart failure

*Greater than 20 percent difference for two to three days over a 10- to 14-day study period were used except for a 15 percent difference being considered positive over seven to ten days in E; length of follow-up scanning was variable in C.

†Treatment regimens were as follows: 5,000 units subcutaneously every 12 hours for studies C and D or every eight hours for B; 5,000 units as an intravenous bolus then 7,500 units subcutaneously every 12 hours (seven days) for A; 5,000 units continuous intravenous infusion every 12 hours (two days) for E.

and congestive heart failure (defined as the presence of an S-3 heart sound, rales or characteristic vascular markings on an x-ray film of the chest) were considered by Pitt and co-workers.[111] Their findings regarding congestive heart failure are presented in Table 3. Concerning this particular study, however, it is difficult to explain how twice as many patients with congestive heart failure and myocardial infarction were "randomized" to a full-dose anticoagulant group as opposed to low-dose heparin and control groups. Nevertheless, in only one of the 14 persons treated with full doses did a positive leg scan develop. Earlier studies of Handley[102,107] had noted benefit from patients receiving full doses, but not low doses of heparin.

Expectant scanning with fibrinogen ^{125}I clearly has a role in studies of deep venous thrombosis, as 92 percent of positive calf scans can be confirmed by venogram; correlation of popliteal and femoral venous involvement fell to 69 percent, however.[114] Since distal disease may be the precursor of more proximal involvement and the latter may embolize to the lung, the relationship is logical. Assuming 32 percent of postmyocardial infarction patients with deep venous thrombi shown by calf scanning can be reduced to 10 percent,[110,111] the uncommon occurrence of pulmonary emboli makes it difficult to establish that treatment is effective. The question remains as to whether the patients in whom pulmonary emboli develop would be among those in whom low doses of heparin failed to cause a response. Some credence to this consideration comes from the study by Brozovic,[115] who gave low doses of heparin subcutaneously to normal subjects and found nearly 5 percent who had no detectable levels even by the most sensitive assays. This percentage may even be higher for patients because acute phase reactants, in addition to other plasma proteins, can bind heparin and presumably compete with antithrombin III to lower the anticoagulant effect of a standardized dose. The risk of bleeding following low-dose heparin administration must also be taken into account, although this risk must be considerably lower than in the use of full-dose anticoagulation. It is of interest that an additional 5 percent of the normal subjects referred to above[115] had sufficient anticoagulant effect to prolong their partial thromboplastin times and would thus have a risk comparable to that of patients receiving higher doses of heparin.

Concerning recommendations that can be drawn from the available data, patients at high risk for venous thromboembolic disease developing, such as those who have congestive heart failure with anticipated prolonged bed rest, and who have no contraindications for anticoagulation, should be treated with full doses. The risk of bleeding clearly needs to be weighed against the risk of clinically significant morbidity from venous thromboembolism. As an option, low doses of heparin may be given to patients at relatively high risk although attention to early ambulation and leg exercising, where possible, may well be at least as important in preventing the relatively uncommon but serious complication of pulmonary embolus. It is hoped that additional data which further delineate as well as give relative weights to specified risk factors will be forthcoming to show if there is a subset of patients who benefit from the low-dose regimen. As with studies on the effects of anticoagulants on mortality and reinfarction discussed above, statistical control of confounding variables (such as age and the severity of congestive heart failure) would lend power to the analyses.

Anticoagulants to Reduce Arterial Embolization From the Heart

Mural Thrombi and Myocardial Infarction

In the three large-scale randomized series examining the effects of anticoagulation on mortality during the first month following myocardial infarction, data on arterial embolic events were also provided (Table 2). Although the number of arterial events was lower in the treated groups in

both the MRC and VAH studies (but not the BMH one) and these numbers reached significance by x^2 analysis, calculating a measure of association to correct for N, one finds extremely weak relationships (ϕ equals 0.07 and 0.06, respectively).

In a series of 783 patients with acute myocardial infarction studied from 1973 through 1976 in Australia, 13 or 1.7 percent had a cerebral vascular accident within an average of six days following the infarction.[116] All but one of these patients had transmural infarction; the latter plus an additional patient were two in whom ventricular aneurysms were present. Creatine kinase elevations were more than eight times normal in all of those with transmural infarction in whom strokes developed. Based on this evidence, routine anticoagulation with heparin and warfarin was begun for all patients with pronounced enzyme elevations and in whom anticoagulants were not contraindicated for other reasons.

Of interest, a study by Hamby and associates[117] dealt with 22 patients in whom left ventricular thrombi were diagnosed by angiography at cardiac catheterization. This corresponded to a frequency of nearly 5 percent in all patients with arteriosclerotic heart disease evaluated during this period. A nearly fivefold increase in incidence of thrombi was noted if only patients with previous transmural, anterior wall infarction were considered. Clinically significant systemic emboli had occurred in 4 of the 22 patients.

Another viewpoint on mural thrombi comes from the surgical experiences with ventricular aneurysms. Considering two recent series[118,119] half to two thirds of these patients were found to have mural thrombi at operation, and in only a quarter to a half of these had the diagnosis been made by preoperative angiography. Strikingly, the incidence of clinically significant systemic arterial emboli was quite low, around 5 percent; furthermore, patients who were receiving orally given, long-term anticoagulants had the same incidence of thrombi as those who were not. A final perspective on postmyocardial infarction as a cause of systemic arterial embolization comes from the series of Satiani and Evans.[120] Over a 12-year period they saw 122 patients with arterial emboli; in 94 of them a cardiac source was identified and a third of these had had a myocardial infarction.

Thus, patients with major transmural myocardial infarction, particularly of the anterior wall, have a much higher risk of ventricular mural thrombi developing. When a ventricular aneurysm is present, one is particularly prone to this complication. In a relatively small percentage of patients with thrombi, clinically significant arterial embolization develops, especially when associated with an aneurysm. It is not yet clear that anticoagulant therapy can lower the risk of embolization, let alone the development of a mural thrombus, and future studies will have to consider high-risk patients and control for multiple risk factors including congestive heart failure and atrial arrhythmias, as discussed below. These studies should assess the development of mural thrombi or their response to anticoagulant therapy once established. As noninvasive techniques, two-dimensional echocardiography and imaging using platelets labeled with indium 111 represent useful tools for such investigations as they appear to show clinically significant thrombi and may even distinguish new from old thrombi.[121]

Atrial Fibrillation and Arterial Embolism

It has been known for some time that the risk of systemic arterial embolism is substantially increased in patients with atrial fibrillation and mitral valve disease. Typically, Adams and coworkers[122] noted that of 42 patients not receiving anticoagulants whose cases were followed in the 1950's, 13 died of cerebral vascular emboli, whereas only 4 of 42 died of this cause in the subsequent decade when all were receiving treatment.

A more recent survey has emphasized risks of embolization and that ischemic (nonvalvular) heart disease now accounts for more than 80 percent of such patients.[123] Several autopsy series have attested to the association and have noted that asymptomatic emboli were considerably more prevalent than those that were clinically recognized. In a series of 333 autopsy studies done between 1962 and 1974 of patients who had died in atrial fibrillation, it was found that essentially half of them (171) had had ischemic heart disease and 59 (35 percent) of these had had clinically significant systemic emboli with pathologic or surgical confirmation.[124] For a control, 58 patients with ischemic heart disease without atrial fibrillation were considered; in only four (7 percent) was systemic arterial embolism found. Nearly three quarters of patients with atrial fibrillation with embolism had involvement of the brain. Furthermore, half of the autopsied patients with atrial fibrillation and emboli had mural thrombi, versus an 8 percent incidence in those

without emboli. Overall, the left atrium was involved nearly four to five times more frequently than the left ventricle in these patients. Of patients with atrial fibrillation, 27 (8 percent) had been receiving anticoagulant therapy and nine of these had embolic events while receiving wärfarin; data as to the degree of anticoagulation, however, were not available in this series.

Questioning the incidence of emboli in a general population, the 20-year follow-up data from the Framingham study are applicable.[125] In considering their population of 5,184 persons, there were 345 episodes of stroke overall and the risk of stroke in patients with atrial fibrillation without rheumatic heart disease (481 person-years, 20 stroke events) constituted a 5.6-fold increased rate compared with controls from the population adjusted for age, blood pressure and sex. Furthermore, it appeared that the difference in frequency of stroke among patients with atrial fibrillation was essentially due to cerebral emboli as the more common atherothrombotic brain infarction, which accounted for 59 percent of all strokes, was equal in the matched groups. For patients who had atrial fibrillation diagnosed after presenting with a stroke or had a stroke preceding the onset of atrial fibrillation these events were considered as unrelated. In this regard, data by Henry and co-workers[126] are of interest in that atrial fibrillation was rare when the left atrial dimension was below 40 mm in diameter (3 of 117 patients) but common when this chamber was enlarged beyond this measurement (80 of 148). These data suggest that left atrial size is an important determinant in the development of atrial fibrillation such that mural thrombi could form in the enlarged chamber and become dislodged either before or, more likely, in association with the onset of atrial fibrillation in some patients. In any event, the strong association between mitral valve disease, left atrial enlargement and atrial filbrillation needs to be considered.

In a study of 100 patients with other sinoatrial arrhythmias persisting an average of ten years, 16 had had systemic arterial emboli and all but one of these had the bradycardia-tachycardia syndrome.[127] Of 712 control patients with complete heart block, embolism occurred in only 1.3 percent whereas 7 percent of 41 patients with chronic ventricular bradycardia and atrial flutter or fibrillation had systemic emboli. Age appeared to increase the risk; all patients in whom emboli occurred were over 54 years of age. Although these authors caution that the risks of anticoagulants, particularly in elderly persons, may contraindicate their use, they suggest routine administration as an attempt to reduce embolic complications.

Arterial Embolism After Valve Replacement

Surgical heart valve replacement has evolved during the past two decades with a variety of types of prosthetic and, more recently, tissue valves being used. Early experience with ball and cage and tilting disc prosthetic devices underscored the need for anticoagulants to minimize arterial thromboembolism after replacement.[128] Advances in engineering design such as cloth covering of the Starr-Edwards valves and a convex-concave modification of the Bjork-Shiley valves have been made in a large part to reduce this risk; the overall risk has been decreased to where it may approach one to two clinically significant arterial emboli per 100 patient years,[129-131] and patients can be expected to survive several years with artificial valve replacement.[132-134] Because most of the clinical embolic events involve the cerebral circulation, the morbidity of this complication is high. Furthermore, it is necessary for these patients to be maintained on regimens of orally given anticoagulants such that they may also have, over the years, a 10 percent risk of having clinically significant bleeding.

A recent series from Great Britain has addressed the problems of patients on long-term regimens of orally given anticoagulants.[135] In following some 500 cases (nearly 1,200 patient-years) between 1970 and 1977, the authors noted 51 hemorrhages in 41 patients where the patients sought medical advice. Half of these hemorrhages were life-threatening and two patients died. Most of the life-threatening bleeding was associated with excess anticoagulation which occurred despite careful monitoring; all but one of the hemorrhages that were not deemed potentially lethal occurred in patients in whom the good anticoagulant range was maintained. Some 60 percent of the patients in this series had prosthetic valves.

In an attempt to further reduce the risks of thromboembolism and those from long-term anticoagulant therapy, tissue valves have been developed. Reitz and associates[136] reported results in 25 patients who had had repeated thromboemboli from prosthetic mitral valves in whom tissue valves had been engrafted. The frequency of emboli was reduced from 66 episodes in 101

patient-years for the prosthetic devices to four episodes in 67 patient-years follow-up for the grafts—a more than tenfold reduction. Furthermore, three of the episodes occurred despite anticoagulation in a single patient who had an extremely large left atrium and persistent atrial fibrillation. Eight of their patients with tissue grafts were able to be followed without anticoagulation.

Although it was hoped that porcine xenografts would circumvent the need for anticoagulation, the report by Edmiston and co-workers[137] noted that of 22 single mitral porcine valve recipients (all but one receiving long-term anticoagulant therapy), atrial emboli occurred in five. Of these, one died and three others had permanent neurological deficits. These authors also examined at autopsy five mitral porcine valves from patients who had not been receiving anticoagulant therapy and noted left atrial thrombi in three and thrombus formation in three at either the interface or the valve cusps. Therefore, particularly for mitral valve disease, it appears that left atrial enlargement and atrial fibrillation remain important risk factors for developing atrial thromboemboli. Indeed, this is the basis for the current rationale in xenograft replacement that has led to a third of all mitral valves replaced in the large Stanford series of patients receiving long-term therapy with orally given anticoagulants. In contrast, in only 9 percent of patients with isolated aortic xenographs was this therapy required.[138]

In the long-term follow-up study of the porcine valves Oyer and associates[138] noted that clinical arterial thromboembolic events occurred 1.7 percent per patient-year in aortic valves as opposed to 2.6 percent per patient-year in mitral valves—which is somewhat better than or at least comparable to the best results with prosthetic devices.[128,129] Similar results have been reported with a different model of porcine xenograph.[139] Bleeding and the less common complication of thrombotic obstruction, particularly of the Bjork-Shiley prosthetic implant, remain higher risks for patients receiving prosthetic as opposed to tissue valves; all patients with the former need long-term chronic anticoagulant therapy. Although experiences have been limited to select surgical teams, it appears that unstented homograft aortic valves[140] or meticulous surgical reconstruction of incompetent mitral valves[141] offers even greater reduction of thromboembolic risk.

A few studies have examined the combination of antiplatelet agents with anticoagulants following cardiac valve replacement. Sullivan and co-workers reported a striking reduction of arterial emboli from 14 percent to 1 percent in a year of follow-up by adding dipyridamole, as opposed to a placebo, to the warfarin therapy. To answer the question of efficacy of antiplatelet therapy alone, a group of patients in whom follow-up of warfarin therapy would have been extremely difficult received only dipyridamole. There was nearly a sixfold increase in incidence (to 30 percent) of thromboembolism compared with other patients to whom warfarin had been prescribed, and 13 or 14 thromboembolism-related fatalities occurred in the dipyridamole-treated group.[143] More recently, Dale and co-workers[144] have looked at the combination of aspirin with oral anticoagulants. The 12 events in the 148 patients given warfarin alone were significantly greater than the 2 events in the same number of patients given warfarin plus aspirin (x^2 equals 7.50, P less than 0.01; ϕ equals 0.16). There was an increased incidence of bleeding in patients receiving aspirin, almost exclusively in bleeding from the gastrointestinal tract.

Additional studies examining combinations of agents are clearly indicated. It is important that other variables such as rhythm and chamber-size, ischemic heart disease with or without anterior myocardial infarction or aneurysm be considered. It is also important (and fortunately, becoming more of a pattern) to report data on long-term follow-up of patients with carefully defined bleeding complications as related to the degree of anticoagulant control. Additional bleeding risk factors (other hemostatic defects, aspirin ingestion, underlying or the unmasking of occult lesions, or hypertension) also need to be considered. In analyzing data by patient years, the variable postoperative intervals have to be considered. Finally, where only events are reported, independence will be violated in any patient who has more than one of the uncommon complications.

Fibrinolytic Therapy After Acute Myocardial Infarction

There has been an extraordinary effort put into the study of fibrinolytic agents in acute myocardial infarction over the past two decades with strikingly little evidence that patients derive any benefit. Theoretically, thrombus dissolution (inasmuch as thrombi and not atheromas occlude coronary vessels) or at least the prevention of extension of infarct size could be affected, though this

rationale is open to question. The multiplicity of problems of study design—including infusion early in the course, which agent is used, for how long and with what end point—have recently been reviewed and some 19 study designs contrasted.[145] Variability in patient populations and protocols undoubtedly accounts for the fact that results are incomparable and anything from reduction of arrhythmias to earlier peaking of enzymes has been claimed and subsequently refuted.

Of the adequately controlled trials, one European cooperative study found no difference in acute or 12-month mortality after urokinase infusion,[146] whereas another European group found a small difference in mortality (x^2 equals 6.45; P less than 0.025; ϕ equals 0.09) at 28 days after streptokinase administration.[147] Trials from the United Kingdom[148] and Australia[149] with 6- and 12-month follow-up, respectively, concluded that overall mortality was unchanged. Indeed a recent European streptokinase trial failed to confirm a significant difference at 28 days,[150] despite the involvement of the same centers which had previously noted the significant difference.[147]

This recent study of streptokinase following acute myocardial infarction[150] deserves further comment as mortality was significantly reduced from 31 percent to 15 percent at six months (x^2 equals 10.32; P less than 0.005; ϕ equals 0.18). In attempting to restrict the target population, they had entered into the study only patients of medium to high risk of mortality and 38 percent of patients so classified were excluded, presumably because of the numerous contraindications to fibrinolytic therapy. This study was then limited to 14 percent of all patients with acute myocardial infarction seen in the 11 different centers during the trial period. Although control and streptokinase-treated groups were comparable even on multivariant analysis of risk factors, there were twice as many patients in the control group who were older than 60 years of age (34 versus 17) and nearly twice as many control patients (62 versus 33) who had more than five ectopic beats per minute on admission. Because this study was designed to examine the subsegment of patients who were at medium to high risk of mortality, one must consider first that most deaths following myocardial infarction occur early. Furthermore, it is not clear why, for example, there were twice as many patients dying who did not have heart failure, previous infarction or tachycardia on admission from the control group as opposed to the streptokinase-treated group. Indeed, these latter findings would suggest that it was those patients with lower risk factors among these groups that were responsible for the reported benefit as opposed to the initial hypothesis and subsequent conclusion that higher risk patients benefit.

It is difficult to reconcile this study's findings to previous experience. Did the overall higher risk group have long-term mortality reduced by the acute streptokinase treatment or was this difference due to some inhomogeneity within the groups to be treated? It would be important to examine their variables such as age as interval rather than grouped data and to consider the possibility of interaction effects (heart failure, previous infarction, abnormal rates or rhythms) upon mortality. Information as to exclusions and follow-up death rates will be helpful when published. Future studies need to be directed at defined subgroups, as attempted in the latest trial but, as with anticoagulant studies, risk factors first need to be controlled. Multivariate analysis, not just to compare groups, can provide a more powerful statistical approach. With the current results, however, any potential benefit of systemic fibrinolytic therapy, which requires a major effort in monitoring to avoid catastrophic complications, remains purely speculative.

Current studies of lower doses of fibrinolytic agents infused directly into recently occluded coronary vessels have shown a dramatic reestablishment of flow. However, the role of these procedures and their risks in the management of acutely ill patients, as well as their long-term results, remain to be evaluated.

Drugs That Modify Platelet Function

JOHN M. HARLAN, MD*

THE RATIONALE for the use of platelet inhibitor therapy in coronary artery disease (CAD) has already been discussed. In the past ten years these theories have been tested in a series of clinical studies involving more than 10,000 patients and costing well over $30,000,000. However, as a recent review stated, ". . . none of the results reported so far are conclusive enough to recom-

*Assistant Professor of Medicine, Division of Hematology, University of Washington.

This work was carried out during tenure of a Clinician-Scientist Award of the American Heart Association with funds contributed in part by the AHA of Washington.

mend any specific regimen."[151] This section will consider the major studies and the reasons for the continuing uncertainty.

The recent studies have employed aspirin, sulfinpyrazone or dipyridamole, whereas several earlier primary and secondary intervention studies evaluated clofibrate and beta-adrenergic blockers. Though intended as a hypolipidemic agent, clofibrate was also reported to affect platelet function in vitro and to prolong platelet survival in vivo.[152,153] The beta-blocker propranolol has been shown to modify the platelet hyperaggregability seen in vitro in some patients with ischemic heart disease.[75,154,155] These effects are of uncertain clinical importance and may not be associated with all beta-antagonists. The trials with both clofibrate and propranolol were not designed to test their efficacy as inhibitors of platelet function and these drugs clearly have major effects other than platelet inhibition; therefore, they will not be considered further in this review.

The use of platelet active drugs in angina has largely been restricted to studies with dipyridamole. More than a dozen studies, most of them uncontrolled, have evaluated the efficacy of the drug as an antianginal agent.[156] The results generally have been inconclusive and are further confused by the drug's action as a coronary vasodilator. None of the studies were large enough or of sufficient duration to evaluate adequately an effect on death or infarction. Recently, there has been great interest in the role of platelets in variant angina characterized by rest pain, ST elevation and angiographic evidence of coronary spasm. Platelet activation and release of the potent vasoconstrictor thromboxane A_2 could theoretically trigger these episodes of coronary vasospasm. Support for this hypothesis comes from studies showing elevation of thromboxane B_2, the stable breakdown product of thromboxane A_2, during episodes of rest pain and ST elevation.[157] However, a recent double-blind crossover study using platelet prostaglandin synthesis inhibitors in these patients did not show any reduction in angina or electrocardiographic changes despite prevention of thromboxane A_2 release.[158] It, therefore, seems more likely that the platelet involvement is secondary.

The major focus of these agents in CAD has been the prevention of recurrent infarction and death. At this point it is important to consider the natural history of CAD and myocardial infarction (MI) and how it relates to the design and interpretation of the intervention trials (Figure 5).[159,160] Each year in the United States alone there are about one million *heart attacks*—a term used here to describe both acute infarction and sudden cardiac death. Nearly 200,000 victims die before admission to hospital and about another 200,000 die in the first month, most of them in the first 24 hours. Of the 400,000 to 500,000 who survive the first month, about 10 percent or 40,000 to 50,000 die in the first year after infarct, generally of sudden death or recurrent infarction. After patients have survived a year, the death rate then stabilizes at 3 percent to 5 percent per year. Thus, therapy producing a 30 percent reduction in secondary cardiac deaths saves about 15,000 lives per year in the United States. The curve (Figure 5) for the normal population shows a yearly cumulative mortality or infarction rate of about 1 percent for a middle-aged cohort. With symptomatic CAD the yearly rate is 3 percent to 5 percent. For patients with an acute *heart attack,* involving both infarction and sudden death syndrome, there is an immediate period of dramatic mortality, mostly in the first 24 hours, so that by one month the cumulative mortality is about 40 percent. During the next six months the rate increases another 7 percent to 8 percent so that by one year another 10 percent have died. To a large extent these curves have determined the patient populations studied in secondary prevention trials in CAD.

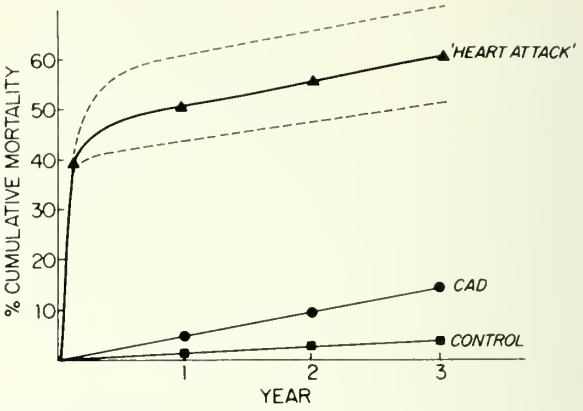


Figure 5.—Cumulative mortality for patients from time of initial "heart attack" (sudden death and/or infarction). High-risk patients have left ventricular dysfunction, anterior infarct and ventricular premature beats. Low-risk patients have none of these. Patients with stable coronary artery disease (CAD) have a 3 percent to 5 percent yearly cumulative mortality while a normal age-matched population has a 1 percent yearly cumulative mortality.

Ideally, one would like to intervene before an

event such as an acute myocardial infarction because it has a rapid initial mortality and the causes of death in the immediate periinfarction period are probably not amenable to therapy with platelet active agents and are only partially modified by out-of-hospital resuscitation efforts and coronary care units. Also, theoretically, these agents might have a better chance to prevent infarction or death or even retard atherosclerosis if given earlier in the disease. However, a primary intervention trial in a normal, unselected population would require 10,000 to 15,000 patients and three to five years to detect a 30 percent reduction in mortality if the frequency of events is about 1 percent. Even in CAD with a 3 percent to 5 percent yearly mortality, 4,000 to 5,000 patient-years would be required to detect a 30 percent reduction. With a death rate of 10 percent in the first year after MI, about 2,000 patient-years are necessary to detect a 30 percent reduction.

Though late in the disease process and already past the most lethal period, survivors of MI are then logistically the most practical study population. The fact that they are also extremely well-motivated and compliant with therapy is also important for study purposes. Figure 5 shows that the prognosis after discharge for MI can be dramatically different when patients are stratified according to certain prognostic factors that have been well defined.[161] The high-risk patients have left ventricular dysfunction, ventricular premature beats and an anterior infarct and their mortality for the first year is about 19 percent. The low-risk group have none of these risk factors and only about a 3 percent mortality in the first year. Obviously, intervention trials need to be well-randomized with respect to these and other important risk factors.

Figure 5 illustrates another important point in the design and interpretation of these trials. The mortality curves following discharge after acute myocardial infarction clearly show an initial period of high mortality in the first six months after which the curve parallels that of patients with CAD. Death is generally by sudden death or recurrent infarction. It is clear that a secondary intervention trial in which patients are enrolled after the first six months has selected a population that has already survived the greatest risk period and the frequency of coronary deaths will be similar to that for other CAD patients—whereas one that enrolls patients in the first weeks postinfarction selects a population initially at higher risk. This issue of entry time has been repeatedly raised in the discussions of the completed trials of secondary prevention of MI.

To date there have been seven large, randomized, double-blind, controlled trials in the secondary prevention of MI and coronary death (Table 4). Smaller trials and case control studies will not be reviewed since they are of anecdotal interest only and served primarily to provoke interest in the field. The *hard* end points measured in most of these studies include total mortality from all causes and coronary mortality; total mortality is most critical because it is possible that therapy could reduce coronary mortality while increasing mortality from other causes and thus produce no change or even an overall increase in total mortality. The primary intervention trial with clofibrate illustrates this point. Though nonfatal infarctions were reduced with clofibrate administration there was a net increase in mortality due to an excess of deaths from biliary and gastrointestinal causes.[162] In most of the trials coronary mortality including sudden deaths and fatal infarctions is also measured. In general about 40 percent of coronary deaths are sudden, 40 percent are due to reinfarction and the remainder are from other cardiac causes; coronary mortality usually comprises 80 percent to 90 percent of the total mortality. Sudden death is usually defined as a natural death due to cardiac causes occurring instantaneously or up to one hour after onset of symptoms.[163] Nonfatal MI is a *softer* end point which is more difficult to define and quantify with certainty in multicenter studies. Coronary incidence combines both coronary mortality and nonfatal MI.

First Medical Research Council Study

The first Medical Research Council Study (MRC I)[164] initially considered patients from the Cardiff area only and was expanded to include other centers when preliminary results of the Boston Collaborative Drug Surveillance Program appeared.[165] Results of the Boston study suggested decreased frequency of myocardial infarction in frequent aspirin users. Though the MRC I showed a trend in favor of aspirin in total deaths, the major benefit was restricted to those patients entered into the study less than six weeks after their myocardial infarction. Most of these patients were from the initial center and therefore the investi-

TABLE 4.—*Prospective, Randomized, Double-blind Trials of Platelet Inhibitors in Secondary Prevention of Myocardial Infarction*

Study	*Entry Time After MI*	*Drug Regimen*	*Follow-up*	*Patients*	*End Points*	*Conclusion*
Medical Research Council 1974 (MRC I)	Average 10 wks	ASA 300 mg once a day	2.5 yrs	624 placebo 615 aspirin	Total death	Trend in favor of ASA *Significant reduction of 40% in mortality with ASA in men entered less than 6 wks post-MI
Coronary Drug Project Aspirin 1976 (CDPA)	Average 7 yrs	ASA 324 mg three times a day	1-2 yrs	758 placebo 771 aspirin	Total death Coronary death Sudden death Nonfatal MI Coronary incidence	Trend in favor of ASA for all events
German-Austrian Multicenter Trial 1977 (German-Austrian)	Under 6 wks	ASA 1.5 grams a day	2 yrs	309 placebo 317 aspirin	Total death Coronary death Nonfatal MI Coronary incidence	Trend in favor of ASA for all events
Medical Research Council 1979 (MRC II)	50% under 7 days	ASA 300 mg three times a day	1 yr	850 placebo 832 aspirin	Total death Coronary death Nonfatal MI Coronary incidence	Trend in favor of ASA in total and coronary deaths *Significant reduction of 34% in nonfatal MI *Significant reduction of 28% in coronary incidence
Anturane Reinfarction Trial 1980 (ART)	25-35 days	Sulfinpyrazone 200 mg four times a day	16 mos	783 placebo 775 sulfinpyrazone	Total death Coronary death Sudden death Nonfatal MI	*Significant reduction in sudden death in first 6 mos, no effect 7-24 mos Borderline significant reduction in total and coronary mortality all due to reduction in sudden death No effect on nonfatal MI
Aspirin Myocardial Infarction Study 1980 (AMIS)	Average 25 mos 85% over 6 mos	ASA 500 mg twice a day	3 yrs	2,257 placebo 2,267 aspirin	Total death Coronary death Sudden death Coronary incidence (nonfatal MI)	No effect of ASA on total, coronary or sudden death or coronary incidence Borderline significant reduction in nonfatal MI and stroke
Persantine Aspirin Reinfarction Study 1980 (PARIS)	2 mos-5 yrs, only 20% under 6 mos	ASA 324 mg three times a day ASA 324 mg three times a day +dipyridamole 75 mg three times a day	44 mos average	406 placebo 810 aspirin 810 combination	Total death Coronary death Coronary incidence Nonfatal MI Sudden death	Trend in favor of ASA or combination for total and coronary mortality and coronary incidence *Significant reduction of 50% in coronary incidence for first two years for combination *In subgroup of patients entered less than 6 mos post-MI significant reduction of 60% at 3 yrs in coronary mortality for combination

ASA = acetylsalicylic acid (aspirin) MI = myocardial infarction NS = not stated but not significant

*Statistically significant by study criteria.

gators could not exclude a geographic rather than time effect.

Coronary Drug Project Aspirin Study

The Coronary Drug Project Aspirin (CDPA) study[166] recruited patients from two previous studies which had been prematurely terminated. It showed a favorable trend for aspirin for both total death and cardiac death and cautiously concluded:

> The observed difference in mortality is suggestive of a beneficial therapeutic effect for aspirin in the secondary prevention of coronary heart disease. However, the numbers of patients studied and the length of follow up for individual patients was not sufficient to draw a definitive conclusion in this regard.

Of note is the fact that most of these patients were entered in the study many years after their infarct.

German-Austrian Study

The German-Austrian cooperative study[167] randomly assigned patients early after their infarction to groups receiving aspirin, placebo or an orally given anticoagulant. Random assignment to aspirin-treated or placebo groups was conducted in a double-blind fashion. Again, there was a trend in favor of the aspirin-treated group for most end points, but statistical significance was not achieved by study criteria. Patients treated with orally given anticoagulants did worse than either the aspirin-treated or placebo groups.

Second Medical Research Council Study

The second Medical Research Council study (MRC II)[168] was conducted specifically to evaluate the effects of aspirin in patients entered early after myocardial infarction. The study was also expanded to include other end points besides total mortality. Again, there was a trend in favor of aspirin for reduction in total mortality, and now there was a significant reduction in nonfatal myocardial infarction and coronary incidence in the aspirin-treated patients. In both the aspirin and the placebo group there was a high withdrawal rate which troubled the investigators but could not be easily explained. They concluded,

> These results are consistent with all the published evidence currently available on the use of aspirin in the prevention of mortality in patients who have had a myocardial infarct. However, the results are not conclusive.

Anturane Reinfarction Trial

The Anturane Reinfarction Trial (ART)[169,170] was sponsored by Ciba-Geigy, the makers of sulfinpyrazone (Anturane), and has certainly been the most controversial. It was first published in 1978 after an eight-month average follow-up when a prescheduled evaluation showed a dramatic difference in the incidence of sudden death. At that time the short-term results were disclosed to investigators and patients and, without breaking the code, the trial was continued with new informed consent. The initial results were heavily criticized for use of a nominal P value, multiple looks at the data, exclusion of "nonanalyzable" deaths and ineligible patients from statistical analysis, and a significantly increased frequency of arrhythmias at entry in the placebo group. However, on follow-up at 16 months, the reduction in sudden death in the sulfinpyrazone-treated group remained highly significant. The effect was apparent only in the first six months of treatment; from 7 to 24 months there was no difference between sulfinpyrazone-treated and placebo groups. Overall there was a borderline significant reduction in total and coronary mortality for the sulfinpyrazone group which was attributable solely to the reduction in sudden death in the first six months. However, when "nonanalyzable" deaths and ineligible patients are included, this reduction in total mortality at 24 months is no longer significant. Sulfinpyrazone treatment had no significant effect on the incidence of nonfatal myocardial infarction or any other end point except sudden death. The mechanism by which sulfinpyrazone might reduce the frequency of sudden death remains speculative. It has been suggested that the drug has antiarrhythmic properties in addition to its platelet inhibitory effects or may act as a protective agent for vascular endothelium.[171,172]

Whatever the mechanism, the results reported in this trial were striking and controversial. Much of the controversy now centers on the definition of sudden death and, hence, classification of deaths in the trial. When an unofficial Food and Drug Administration audit of the study reclassified half of the deaths, there was no longer any significant benefit from administration of sulfinpyrazone.[173] Also, the trial was not initially designed to test the hypothesis that the platelet inhibitory agent sulfinpyrazone would reduce the frequency of sudden death in myocardial infarction survivors. This result was totally unexpected. Strictly speaking, a trial can only prove the original hypothesis. Any other finding remains speculation, which although important in provoking further trials, cannot be considered to have

been proved by the trial. The final judgment of the Food and Drug Administration was that the case for sulfinpyrazone was not persuasive and it was not approved as a drug for the prevention of sudden death.

Aspirin Myocardial Infarction Study

The Aspirin Myocardial Infarction Study (AMIS)[174] was a National Heart, Lung and Blood Institute sponsored multicenter, randomized, double-blind trial involving the largest number of patients. Most of the patients were entered in the study more than six months after their first infarction. Unlike the other trials, AMIS showed no trend in favor of aspirin for reduction in total or coronary mortality. Similarly, sudden death was unaffected by aspirin treatment. There was some reduction in nonfatal myocardial infarction and stroke; however, it was not significant by study criteria. This well-designed and well-executed study clearly showed that aspirin administration at 1 gram per day, begun six months after the first myocardial infarction, was of no benefit. This is in contrast to the trend suggested by the Coronary Drug Project which also enrolled patients late after myocardial infarction with a similar aspirin dose. The major criticism of both these studies has centered on the fact that the patients were enrolled late after their infarction, and, thus, the studies would not have detected a beneficial effect on early mortality.

Persantine-Aspirin Reinfarction Study

The most recent study is the Persantine-Aspirin Reinfarction Study (PARIS)[175] sponsored by Boehringer-Ingelheim, the makers of dipyridamole (Persantine). Patients were randomly assigned to groups receiving placebo, aspirin or the combination of aspirin and dipyridamole. Again, a trend in favor of aspirin or the combination in coronary mortality or coronary incidence was noted. Indeed, the combination reduced coronary incidence significantly during the first two years. Of importance is the fact that in a subgroup of patients who were entered less than six months after infarction there was a reduction during 36 months in coronary mortality with administration of the combination.

Table 4 summarizes the results of these seven randomized, double-blind studies of platelet-modifying drugs in the secondary prevention of myocardial infarction. With the exception of the AMIS trial, there is a trend in favor of antiplatelet agents in all the trials. While this trend may be sufficient to prompt individual physicians to recommend antiplatelet agents for their patients after myocardial infarction, it does not warrant a general recommendation for the use of any single or combination platelet-modifying regimen in the secondary prevention of myocardial infarction.

There are a number of explanations for the inconclusive results of these trials. It is possible that the coronary event, whether it be sudden death or myocardial infarction, is not platelet-mediated and thus would not be affected by the use of platelet-modifying agents. Even if platelets play a critical role in these events, the antiplatelet therapy currently used, whether it be single agent or combination regimens, may be inadequate. As previously mentioned, the entry time after infarction may be critical since most of the deaths occur in the first six months after infarct. Theoretically, the aspirin dose used may be important since larger or frequent doses of aspirin may impair prostacyclin (PGI_2) production by the vessel wall in addition to inhibiting thromboxane production by platelets.[176,177] The importance of the aspirin dose remains purely speculative, however, since no dose response result was noted between MRC I (300 mg once a day) and MRC II (300 mg three times a day).

Because of the time, expense and resources involved it will be several years before newly designed trials of antiplatelet agents in the secondary prevention of myocardial infarction can be completed. In view of the present controversy an additional study to test the effect of sulfinpyrazone on sudden death has high priority. A second dipyridamole-aspirin combination study with early entry after infarction is already planned. There is also interest in reassessing low-dose aspirin therapy in a future trial. When or if such trials will be carried out is as yet uncertain. In the meantime, individual physicians will have to make decisions based on the current, inconclusive information.

REFERENCES

1-80. See part I, March 1981 issue.

81. Rosenberg RD, Lam L: Correlation between structure and function of heparin. Proc Natl Acad Sci USA 76:1218-1222, 1979

82. Rosenberg RD: Chemistry of hemostatic mechanism and its relationship to the action of heparin. Fed Proc 36:10-18, 1977

83. Holmer E, Soderstrom G, Andersson LO: Studies on the mechanism of the rate-enhancing effect of heparin on the thrombin-antithrombin III reaction. European J Biochem 93:1-5, 1979

84. Stenflo J: Vitamin K, prothrombin and γ-carboxyglutamic acid. N Engl J Med 296:624-626, 1977

85. Friedman PA, Rosenberg RD, Hauschka PV, et al: A spectrum of partially carboxylated prothrombins in the plasma of coumarin treated patients. Biochim Biophys Acta 494:271-276, 1977

86. Thompson AR: Factor IX antigen by radioimmunoassay—Abnormal factor IX protein in patients on warfarin therapy and with hemophilia B. J Clin Invest 59:900-910, 1977

87. Castellino FJ, Violand BN: The fibrinolytic system—Basic considerations. Prog Cardiovasc Dis 21:241-254, 1979

88. Aoki N: Natural inhibitors of fibrinolysis. Prog Cardiovasc Dis 21:267-286, 1979

89. Bell WR, Meek AG: Guidelines for the use of thrombolytic agents. N Engl J Med 301:1266-1270, 1979

90. Drapkin A, Merskey C: Anticoagulant therapy after acute myocardial infarction. JAMA 222:541-548, 1972

91. Modan B, Shani M, Schor S, et al: Reduction of hospital mortality from acute myocardial infarction by anticoagulant therapy. N Engl J Med 292:1359-1362, 1975

92. Tonascia J, Gordis L, Schmerler H: Retrospective evidence favoring use of anticoagulants for myocardial infarctions. N Engl J Med 292:1362-1366, 1975

93. Szklo M, Tonascia JA, Goldberg R, et al: Additional data favoring use of anticoagulant therapy in myocardial infarction. JAMA 242:1261-1264, 1979

94. Ravid M, Kleiman N, Shapira J, et al: Anticoagulant therapy in acute myocardial infarction: Demonstration of a selection bias in a retrospective study. Thromb Res 18:753-757, 1980

95. Chalmers TC, Matta RJ, Smith H Jr, et al: Evidence favoring the use of anticoagulants in the hospital phase of acute myocardial infarction. N Engl J Med 297:1091-1096, 1977

96. Goldman L, Feinstein AR: Anticoagulants and myocardial infarction. Ann Intern Med 90:92-94, 1979

97. Lee KL, McNeer JF, Starmer CF, et al: Clinical judgment and statistics—Lessons from simulated randomized trial in coronary artery disease. Circulation 61:508-515, 1980

98. Frishman WH, Ribner HS: Anticoagulation in myocardial infarction: Modern approach to an old problem. Am J Cardiol 43:1207-1213, 1979

99. Merskey C, Drapkin A: Long-term anticoagulant therapy after myocardial infarction. JAMA 230:208-209, 1974

100. Overall JE: Power of chi-square tests of 2×2 contingency tables with small expected frequencies. Psychol Bull 87:132-135, 1980

101. Walsh PN, Stengel JM, Sherry S: Synopsis, summary, conclusions and recommendations. Circulation 57 & 58(Suppl II):7-12, 1973

102. Handley AJ, Emerson PA, Fleming PR: Heparin in the prevention of deep vein thrombosis after myocardial infarction. Br Med J 2:436-438, 1972

103. Habersberger PG, Pitt A, Anderson ST: Venous thromboses in myocardial infarction—Comparison in heparin dosage. Br Heart J 35:538-542, 1973

104. Murray TS, Lorimer AR, Cox FC, et al: Leg-vein thrombosis following myocardial infarction. Lancet 2:792-793, 1970

105. Nicolaides AN, Kakkar VV, Renney JTG, et al: Myocardial infarction and deep-vein thrombosis. Br Med J 1:432-434, 1971

106. Maurer BJ, Wray R, Shillingford JP: Frequency of venous thrombosis after myocardial infarction. Lancet 2:1385-1387, 1971

107. Handley AJ: Low-dose heparin after myocardial infarction. Lancet 2:623-624, 1972

108. Gallus AS, Hirsh J, Tuttle RJ, et al: Small subcutaneous doses of heparin in prevention of venous thrombosis. N Engl J Med 288:545-551, 1973

109. Warlow C, Beattie AG, Terry G, et al: A double-blind trial of low doses of subcutaneous heparin in the prevention of deep-vein thrombosis after myocardial infarction. Lancet 2:934-936, 1973

110. Emerson PA, Marks P: Preventing thromboembolism after myocardial infarction: Effect of low-dose heparin or smoking. Br Med J 1:18-20, 1977

111. Pitt A, Anderson ST, Habersberger PG, et al: Low dose heparin in the prevention of deep-vein thromboses in patients with acute myocardial infarction. Am Heart J 99:574-578, 1980

112. Simmons AV, Sheppard MA, Cox AF: Deep venous thrombosis after myocardial infarction—Predisposing factors. Br Heart J 35:623-625, 1973

113. Cristal N, Stern J, Ronen M, et al: Identifying patients at risk for thromboembolism—Use of ^{125}I-labeled fibrinogen in patients with acute myocardial infarction. JAMA 236:2755-2757, 1976

114. Hull R, Hirsh J: Diagnosis of venous thrombosis by invasive and non-invasive techniques, *In* Joist JH, Sherman LA (Eds): Venous and Arterial Thrombosis—Pathogenesis, Diagnosis, Prevention and Therapy. New York, Grune & Stratton, 1979, pp 33-56

115. Brozovic M, Stirling Y, Abbosh J: Plasma heparin levels after low dose subcutaneous heparin in patients undergoing hip replacement. Br J Haematol 31:461-466, 1975

116. Thompson PL, Robinson JS: Stroke after acute myocardial infarction: Relation to infarct size. Br Med J 2:457-459, 1978

117. Hamby RI, Wisoff BG, Davison ET, et al: Coronary artery disease and left ventricular mural thrombi: Clinical, hemodynamic and angiocardiographic aspects. Chest 66:488-494, 1974

118. Swan HJC, Magnusson PT, Buchbinder NA, et al: Aneurysm of the cardiac ventricle—Its management by medical and surgical intervention. West J Med 129:26-40, Jul 1978

119. Simpson MT, Oberman A, Kouchoukos NT, et al: Prevalence of mural thrombi and systemic embolization with left ventricular aneurysm—Effect of anticoagulation therapy. Chest 77:463-469, 1980

120. Satiani B, Evans WE: Immediate prognosis and five-year survival after arterial embolectomy following myocardial infarction. Surg Gynecol Obstet 150:41-44, 1980

121. Stratton JR, Ritchie JL, Hamilton GW, et al: Left ventricular thrombi: In vivo detection by indium-111 platelet imaging and two dimensional echocardiography. Am J Cardiol (in press) 1981

122. Adams GF, Merrett JD, Hutchinson WM, et al: Cerebral embolism and mitral stenosis: Survival with and without anticoagulants. J Neurol Neurosurg Psychiatry 37:378-383, 1974

123. Fisher CM: Reducing risks of cerebral embolism. Geriatrics 34:59-61; 65-66, 1979

124. Hinton RC, Kistler JP, Fallon JT, et al: Influence of etiology of atrial fibrillation on incidence of systemic embolism. Am J Cardiol 40:509-513, 1977

125. Wolf PA, Dawber TR, Thomas HE, et al: Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: The Framingham study. Neurology 28:973-977, 1978

126. Henry WL, Morganroth J, Pearlman AS, et al: Relation between echocardiographically determined left atrial size and atrial fibrillation. Circulation 53:273-279, 1976

127. Fairfax AJ, Lambert CD, Leatham A: Systemic embolism in chronic sinoatrial disorder. N Engl J Med 295:190-192, 1976

128. Borst HG, Papagiannakis N, Beddermann C, et al: Cardiac valve replacement—Problems solved and unsolved. Thorac Cardiovasc Surgeon 27:76-84, 1979

129. Bjork VO, Henze A: Ten years' experience with the Bjork-Shiley tilting disc valve. J Thorac Cardiovasc Surg 78:331-342, 1979

130. Bharadwaj B, Wall R, Nutting S: Long-term follow-up of patients who underwent single valve replacement with Bjork-Shiley prosthesis. Can J Surg 23:183-186, 1980

131. Schoevaerdts JC, Jaumin P, Ponlot R, et al: Twelve year results with a caged-ball mitral prosthesis. Thorac Cardiovasc Surgeon 27:45-47, 1979

132. Thomsen PB, Alstrup P: Thromboembolism in patients without anticoagulants after aortic valve replacement with the Lillehei-Kaster disc valve. J Thorac Cardiovasc Surg 27:313-325, 1979

133. Henry WL, Bonow RO, Borer JS, et al: Evaluation of aortic valve replacement in patients with valvular aortic stenosis. Circulation 61:814-825, 1980

134. Rahimtoola SH: Valve replacement should not be performed in all asymptomatic patients with severe aortic incompetence. J Thorac Cardiovasc Surg 79:163-172, 1980

135. Forfar JC: A 7-year analysis of haemorrhage in patients on long-term anticoagulant treatment. Br Heart J 42:128-132, 1979

136. Reitz BA, Stinson EB, Griepp RB, et al: Tissue valve replacement of prosthetic heart valves for thromboembolism. Am J Cardiol 41:512-515, 1978

137. Edmiston WA, Harrison EC, Duick GF, et al: Thromboembolism in mitral porcine valve recipients. Am J Cardiol 41:508-511, 1978

138. Oyer PE, Stinson EB, Reitz BA, et al: Long-term evaluation of the porcine xenograft bioprosthesis. J Thorac Cardiovasc Surg 78:343-350, 1979

139. Jamieson WRE, Janusz MT, Munro AI, et al: Early clinical experience with the Carpentier-Edwards porcine heterograft cardiac valve. Can J Surg 23:132-137, 1980

140. Thompson R, Yacoub M, Ahmed M, et al: The use of "fresh" unstented homograft valves for replacement of the aortic valve—Analysis of 8 years' experience. J Thorac Cardiovasc Surg 79:896-903, 1980

141. Carpentier A, Chauvaud S, Fabiani JN, et al: Reconstructive surgery of mitral valve incompetence—Ten-year appraisal. J Thorac Cardiovasc Surg 79:338-348, 1980

142. Sullivan JM, Harken DE, Gorlin R: Pharmacologic control of thromboembolic complications of cardiac-valve replacement. N Engl J Med 284:1392-1394, 1971

143. St John Sutton MG, Miller GAH, Oldershaw PJ, et al: Anticoagulants and the Bjork-Shirley prosthesis experience of 390 patients. Br Heart J 40:558-562, 1978

144. Dale J, Myhre E, Loew D: Bleeding during acetylsalicylic acid and anticoagulant therapy in patients with reduced platelet reactivity after aortic valve replacement. Am Heart J 99:746-752, 1980

145. Duckert F: Thrombolytic therapy in myocardial infarction. Prog Cardiovasc Dis 21:342-350, 1979

146. A European Collaborative Study: Controlled trial of urokinase in myocardial infarction. Lancet 2:624-626, 1975

147. European Working Party: Streptokinase in recent myocardial infarction: A controlled multicenter trial. Br Med J 3: 325-331, 1971

148. Aber CP, Bass NM, Berry CL, et al: Streptokinase in acute myocardial infarction: A controlled multicentre study in the United Kingdom. Br Med J 2:1100-1104, 1976

149. Australian Multicentre Trial of Streptokinase in Acute Myocardial Infarction. Med J Aust 1:553, 1977

150. European Cooperative Study Group for Streptokinase Treatment in Acute Myocardial Infarction: Streptokinase in acute myocardial infarction. N Engl J Med 301:797-802, 1979

151. The Medical Letter: Antiplatelet drugs after myocardial infarction. 22:25-26, 1980

152. Gilbert JB, Mustard JF: Some effects of atromid on platelet economy and blood coagulation in man. J Atheroscler Res 3:623-633, 1963

153. Carvalho ACA, Colman RW, Lees R: Clofibrate reversal of platelet hypersensitivity in hyperbetalipoproteinemia. Circulation 50:570-574, 1974

154. Frishman WH, Weksler BB, Christodoulou JP, et al: Reversal of abnormal platelet aggregability and change in exercise tolerance in patients with angina pectoris following oral propranolol. Circulation 50:887-898, 1974

155. Weksler BB, Gillick M, Pink J: Effect of propranolol on platelet function. Blood 49:185-196, 1977

156. Genton E, Gent M, Hirsh J, et al: Platelet-inhibiting drugs in the prevention of clinical thrombotic disease. N Engl J Med 293:1236-1240, 1975

157. Lewy RI, Wierner L, Smith JB, et al: Measurements of plasma thromboxane in peripheral blood of Prinzmetal's angina patients. Circulation 59 & 60(Suppl II):248, 1979

158. Robertson D, Maas RL, Roberts LJ II, et al: Anti-platelet agents in vasospastic angina: A double-blind cross-over study. Clin Res 28:242A, 1980

159. Hurst JW, Logue RB, Walter PF: The clinical recognition and management of coronary atherosclerotic heart disease, *In* Hurst JW, Logue RB, Schlant RC, et al (Eds): The Heart. New York, McGraw-Hill, 1978, pp 1216-1219

160. Armstrong A, Duncan B, Oliver MF, et al: Natural history of acute coronary heart attacks—A community study. Br Heart J 34:67-80, 1972

161. Davis HT, DeCamilla J, Bayer LW, et al: Survivorship patterns in the posthospital phase of myocardial infarction. Circulation 60:1252-1258, 1979

162. Report from the Committee of Principal Investigators: A co-operative trial in the primary prevention of ischaemic heart disease using clofibrate. Br Heart J 40:1069-1118, 1978

163. Moss AJ: Prediction and prevention of sudden cardiac death. Annu Rev Med 31:1-14, 1980

164. Elwood PC, Cochrane AL, Burr ML, et al: A randomized controlled trial of acetyl salicylic acid in the secondary prevention of mortality from myocardial infarction. Br Med J 1:436-440, 1974

165. Boston Collaborative Drug Surveillance Group: Regular aspirin intake and acute myocardial infarction. Br Med J 1:440-443, 1974

166. The Coronary Drug Project Research Group: Aspirin in coronary heart disease. J Chron Dis 29:625-642, 1976

167. Breddin K, Oberla K, Walter E: German-Austrian multicenter two years prospective study on the prevention of secondary myocardial infarction by ASA in comparison to phenprocoumon and placebo. Thrombos Haemostasis 38:168, 1977

168. Elwood PC, Sweetnam PM: Aspirin and secondary mortality after myocardial infarction. Lancet 2:1314-1315, 1979

169. The Anturane Reinfarction Trial Research Group: Sulfinpyrazone in the prevention of cardiac death after myocardial infarction—The Anturane Reinfarction Trial. N Engl J Med 298: 289-295, 1978

170. The Anturane Reinfarction Trial Research Group: Sulfinpyrazone in the prevention of sudden death after myocardial infarction. N Engl J Med 302:250-256, 1980

171. Harker LA, Ross R, Harlan JM, et al: Pharmacologic prevention of endothelial cell injury and homocysteine-induced arteriosclerosis. (Submitted) 1981

172. Moschos C, Escobinas A, Jorgenson D, et al: Effect of sulfinpyrazone on survival following experimental non-thrombotic coronary occlusion. Am J Cardiol 43:372, 1979

173. Kolata GB: FDA says no to anturane. Science 208:1130-1132, 1980

174. Aspirin Myocardial Infarction Study Research Group: A randomized, controlled trial of aspirin in persons recovered from myocardial infarction. JAMA 243:661-669, 1980

175. The Persantine-Aspirin Reinfarction Study Research Group: Persantine and aspirin in coronary heart disease. Circulation 62: 449-461, 1980

176. Jaffe EA, Weksler BB: Recovery of endothelial cell prostacyclin production after inhibition by low doses of aspirin. J Clin Invest 63:532-535, 1978

177. Masotti G, Galanti G, Poggesi L, et al: Differential inhibition of prostacyclin production and platelet aggregation by aspirin. Lancet 2:1213-1216, 1979

Refer to: Hess DS: Newer antiarrhythmic drugs—Medical Staff Conference, University of California, San Francisco. West J Med 134:333-341, Apr 1981

Newer Antiarrhythmic Drugs

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr, Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR. SLEISENGER:* *The topic of this conference is newer antiarrhythmic drugs and our discussant is Dr. David Hess.*

DR. HESS:† The need for newer antiarrhythmic drugs has never been more apparent. For decades physicians have sought an antiarrhythmic agent that had an extended half-life, a minimum of side effects and excellent clinical effectiveness, but such an ideal antiarrhythmic drug is not yet available.

In cardiac care newer antiarrhythmic agents are required for two general clinical uses. First, they are needed in the treatment of supraventricular tachycardia. The management of supraventricular tachyarrhythmias has improved with the introduction of β-adrenergic blocking agents. However, both propranolol and digoxin may be ineffective in controlling supraventricular arrhythmias in situations such as episodes of paroxysmal supraventricular tachycardia (PSVT), atrial fibrillation and atrial flutter in patients with chronic lung disease or congestive heart failure. Hence, nontoxic, effective antiarrhythmic drugs are needed to manage these conditions appropriately.

Second, newer antiarrhythmic drugs are needed for the treatment of ventricular arrhythmias. The comprehensive evaluation and treatment of atherosclerotic coronary artery disease in the 1970's resulted in the development of paramedically manned mobile cardiac units and widespread instruction in cardiopulmonary resuscitation. These factors are now responsible for a significant number of patients surviving out-of-hospital cardiac arrest. However, because there is a high incidence of recurrence of cardiac arrest in this group of patients,[1-3] physicians have learned that aggressive management of these arrhythmias is required. In addition, findings of epidemiologic studies carried out in the 1970's indicate that patients are at a higher risk for sudden cardiac death if they have survived acute myocardial infarction and demonstrate certain premature ventricular depolarization (PVD) patterns during ambulatory monitoring.[4,5] Although it has not been proved conclusively that suppression of arrhythmias will prevent sudden death, it appears prudent to institute therapy with antiarrhythmic drugs in these patients. However, quinidine, procainamide and disopyramide are not always effective in controlling these ventricular arrhythmias and often are associated with significant side effects. Thus, newer antiarrhythmics are needed to supplement the treatment of arrhythmias in these patients with coronary artery disease.

In reviewing the world literature, one notes that there are some 20 antiarrhythmic drugs that are available in other parts of the world but which are not readily accessible in the United States. About ten of these agents are available on experi-

*Marvin H. Sleisenger, MD, Professor and Vice-Chairman, Department of Medicine; Chief of the Medical Service, Veterans Administration Hospital, San Francisco.

†David S. Hess, MD, Assistant Professor of Medicine.

ABBREVIATIONS USED IN TEXT

AV = atrioventricular
PSVT = paroxysmal supraventricular tachycardia
PVD = premature ventricular depolarization
SA = sinoatrial
SVT = supraventricular tachycardia

mental protocols, and four of the most promising medications are discussed here in detail. For completeness, other experimental antiarrhythmic drugs are included in Tables 1 through 3 but will not be reviewed in the text.

Verapamil

Verapamil is a papaverine derivative that was first developed in West Germany in 1962. Initially, it was used as an antianginal agent in Western European countries. However, not long after its release, verapamil was found to have unique electrophysiological properties and proved very effective in treating a variety of supraventricular arrhythmias.

To understand verapamil's antiarrhythmic actions, the cardiac cellular transmembrane potential will be reviewed. The fast response action potential (Figure 1A) is found in the peripheral nerves, in skeletal muscle and within the heart. This action potential is dependent on rapid sodium influx across the channels in the cellular

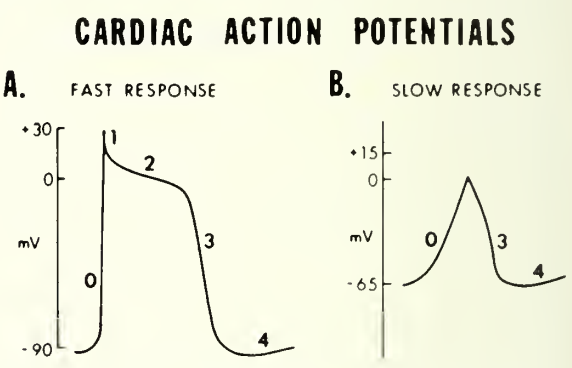


Figure 1.—A. Cellular transmembrane potential of a fast response cell. The action potential is characterized by its rapid upstroke (0), overshoot (1), plateau phase (2), repolarization (3) and slow diastolic depolarization (4). **B.** Cellular transmembrane potential of a slow response cell, characterized by slow upstroke (0), repolarization (3) and diastolic depolarization (4).

TABLE 1.—*Electrophysiological Characteristics of Seven Experimental Antiarrhythmic Drugs in Animal Studies**†*

Drug	*APA*	*APD*	*dV/dt*	*MDP*	*ERP*	*Cond Vel*	*Normal Phase 4*	*Memb Resp*	*ET*	*VFT*	*Contractility*	*Ca++ Current*
Verapamil	0	↓	0	0	0	0	↓	0	..	0	↓	Inhibit
Encainide	0	↓	↓	0	↑	↓	↓	..	0	?	0↓	0
Tocainide	0	↓	0↓	0	↓	↓	↓	↓	↑	↑	..	0
Amiodarone	0	↑	0↓	0	↑	↓	0	↓	..	..	↓	..
Aprindine	0	↓	↓	0	↓	↓	↓	↓	↑	↑	↓	0
Ethmozin	↓	↓	↓	0↓	↓	↓	0	↓	↑	0	↑then↓	0
Mexilitine	0	↓	↓	0	↓	↓	↓	↓	↑	↑	↓	0

↑ = increase; ↓ = decrease; 0 = no change; 0↑ or 0↓ = slight increase or slight decrease, respectively; APA = action potential amplitude; APD = action potential duration; Ca^{++} current = slow current or slow response; Cond Vel = conduction velocity; dV/dt = rate of rise upstroke (phase 0) of action potential; ERP = effective refractory period; ET = excitability threshold; MDP = maximal diastolic potential; VFT = ventricular fibrillation threshold

*Results presented may vary according to tissue type, experimental conditions and drug concentration. Animal data are from "fast-response" type fibers.
†Adapted from Zipes and Troup.[17]

TABLE 2.—*Electrophysiological Characteristics of Seven Experimental Antiarrhythmic Drugs in Human Studies**†*

Drug	*Sinus Rate*	*PR*	*QRS*	*QT*	*A-H*	*H-V*	*ERP-AVN*	*ERP-HPS*	*ERP-A*	*ERP-V*
Verapamil	↓	↑	0	0	↑	0	↑	0	0	0
Encainide	0	↑	↑	↑	0	↑	0	↑	0	0
Tocainide	0↓	0	0	0↓	0↑	0	↓	..	↓	↓
Amiodarone	↓	↑	↑	↑	↑	0	↑	↑	↑	↑
Aprindine	↓	↑	↑	0↑	↑	..	↑	↑	↑	↑
Ethmozin	0↓	0↑	0↑	0	..	..	..	..	..	..
Mexilitine	0	0	0	0	0↑	0↑	0↑	0↑	0	0

↑ = increase; ↓ = decrease; 0 = no change; 0↑ or 0↓ = slight increase or slight decrease, respectively; A = atrium; AVN = atrioventricular node; ERP = effective refractory period; HPS = His-Purkinje system, V = ventricle

*Results presented may vary according to tissue type, experimental conditions and drug concentration.
†Adapted from Zipes and Troup.[17]

TABLE 3.—*Clinical Characteristics of Seven Experimental Antiarrhythmic Drugs**

Drug	*Intravenous*	*Oral*	*Effective Serum or Plasma Concentration (μg/ml)*	*Elimination Half-Life (hr)*	*Absorption*	*Metabolic Secretion Route*	*Side Effects*	*Onset of Action*	
								Intravenous (min)	*Oral (hr)*
Verapamil	0.075-0.15 mg/kg	Maintenance: 80-120 mg q 8 hr or q 6 hr	..	3-7	Good	Hepatic	Neurologic Gastrointestinal Cardiovascular	<5	1-2
Tocainide	0.5-0.75 mg/kg/min for 15 min	Loading: 400-600 mg Maintenance: 400-800 mg q 8 hr	3.5-10	10-17	Good	Renal 40% Probably hepatic 60%	Neurologic Gastrointestinal Cardiovascular	5-10	1-1/2
Encainide	0.9 mg/kg over 15 min	25-75 mg q 6 hr	2-56 ng/ml	3.4	Good	Hepatic	Tinnitus Headache Dizziness	5-10	1-2
Amiodarone ..	5-10 mg/kg	Maintenance: 200-800 mg	..	..	Fair	..	Ophthalmologic Endocrine Neurologic Dermatologic Cardiovascular	5-10	4-6
Aprindine	200 mg at 2 mg/min; 30 min later 100 mg at 2 mg/min; 6 hr later, 100 mg at 2 mg/min	Loading: 100 mg q 6 hr, day 1 75 mg q 6 hr, day 2 50 mg q 6 hr, day 3 Maintenance: 25-50 mg q 8 hr or q 12 hr	1-3	20-30	Good	Hepatic	Neurologic Gastrointestinal Hematologic Cardiovascular	5-10	2
Ethmozin	Loading: 1-3 mg/kg†	Maintenance: 75-150 mg q 6 hr‡	0.5-1.0	5-10‡	Good	Probably hepatic†	Neurologic Gastrointestinal Cardiovascular	<5†	2†
Mexilitine	Loading: 1,200 mg/12 hr; Maintenance: 250-500 mg/12 hr	Loading: 400-600 mg Maintenance: 200-300 mg q 8 hr	0.5-2.0	10-26	Good	Probably hepatic	Neurologic Gastrointestinal Cardiovascular	<5	1-2

q = every

*Adapted from Zipes and Troup.[17]

†Animal data.

‡According to studies in progress, maintenance doses may be in the range of 250 mg every 8 hours and provide a slightly longer half-life.

membrane. The potential is characterized by a rapid upstroke, overshoot and plateau phase before repolarization. This particular type of action potential occurs in atrial and ventricular muscle and in the cells of the His-Purkinje system. However, the sinoatrial (SA) node and the atrioventricular (AV) node do not have fast response action potentials when studied by microelectrode techniques. Instead, they have an action potential depicted in Figure 1B—a slow response action potential. This action potential differs from the fast response in that the depolarization demonstrates a slowed upstroke and absence of an overshoot and plateau phase. Experimental models have shown that a slow influx of calcium ions (and perhaps sodium ions) is responsible for generating this action potential. These ionic calcium currents are blocked by verapamil.[6] Because the AV and SA nodes depend on the slow response action potential for excitation and conduction, medications that specifically inhibit calcium transport will increase the refractoriness and decrease the conduction velocity of these tissues. These electrophysiological properties of verapamil form the basis for its antiarrhythmic action (Tables 1 and 2).

The clinical pharmacology of verapamil is outlined in Table 3. Briefly, it is rapidly and completely absorbed from the gastrointestinal tract, excreted by way of hepatic metabolism and has a half-life of approximately six hours. The hemodynamic effects of verapamil on normal volunteers have been examined in several studies.[6,7] Normal subjects exhibit a primary decrease in systemic vascular resistance and a compensatory increase in heart rate and cardiac output. The left ventricular end-diastolic pressure does not change in these volunteers after verapamil administration. In patients with congestive heart failure, verapamil has two primary opposing effects.[8] By decreasing systemic vascular resistance it may increase cardiac output without a change in heart rate. This "afterload reduction" effect of verapamil, however, can be cancelled by the drug's direct negative inotropic effect on the myocardium. Hence, hemodynamic changes in patients with left ventricular dysfunction may be variable after verapamil administration.

Because verapamil inhibits the slow calcium currents, there is a preferential effect on the SA and AV nodes. Thus, verapamil is most effective clinically in treating arrhythmias that involve the SA and AV node. For example, patients with atrial fibrillation or atrial flutter with rapid ventricular response are excellent candidates for verapamil therapy because the drug slows conduction in the AV node. Verapamil is effective in AV nodal reentrant tachycardia for the same reasons. The effectiveness of verapamil in treating supraventricular arrhythmias has been evaluated by numerous studies in Western Europe and South America; the following review is a composite of 134 clinical studies of this drug.[9]

In assessing verapamil's effectiveness in supraventricular tachycardia (SVT), the above studies usually included patients presenting with a narrow complex tachyarrhythmia, but who had no underlying organic heart disease. Most of these patients had either AV nodal reentrant tachycardia or tachycardia involving an AV bypass tract (Wolff-Parkinson-White syndrome). A total of 1,607 patients with paroxysmal SVT were treated with verapamil given intravenously.[9] In 81 percent of the patients conversion to normal sinus rhythm occurred after the administration of a 10-mg intravenous bolus of the drug. An additional 9 percent of patients were judged to have a good clinical response because of a significant reduction in the SVT rate. Overall, approximately 90 percent of patients responded to this mode of treatment. This remarkable response has not been previously documented with any of the antiarrhythmic drugs now available in the United States.

Verapamil's effectiveness in controlling atrial fibrillation with a rapid ventricular response rate was assessed in 65 clinical studies.[9] The drug was given as an intravenous injection (10 to 20 mg) to 1,474 patients and in 16 percent conversion to normal sinus rhythm occurred. However, the important finding was a significant reduction in the ventricular response rate in 78 percent of the patients. A significant rate reduction was defined as a 30 percent decrease in the ventricular response or a reduction in rate to less than 100 beats per minute. In total, 94 percent of patients with atrial fibrillation responded to the intravenous administration of verapamil. The clinical results of treating patients with atrial flutter have been similar—85 percent of the patients treated had either a significant reduction in ventricular rate or conversion to normal sinus rhythm.[9] The response of these two types of atrial arrhythmias is especially important because digoxin is ineffective in many patients and propranolol is con-

traindicated in those with chronic lung disease or congestive heart failure. Hence, the addition of a safe, rapid-acting antiarrhythmic agent that reduces the ventricular response rate is an important addition to drugs now available.

Although digoxin and propranolol therapy and cardioversion are often effective in treating patients with atrial fibrillation or atrial flutter and rapid ventricular response, verapamil's rapid effectiveness in these same patients provides clinicians with an added dimension in treating certain subgroups of patients. For example, Hagemeijer[10] studied 16 patients with acute myocardial infarction who had either atrial fibrillation or atrial flutter with a rapid ventricular response. These patients had no clinical evidence of congestive heart failure, and the arrhythmias occurred within the first 72 hours of infarction. The arrhythmias were treated with titrated doses of intravenously given verapamil (average dose 10 mg) over a ten-minute interval. Eight patients had atrial fibrillation with an average ventricular rate of 160 beats per minute before treatment. Ten minutes after the administration of verapamil, the average ventricular rate was approximately 100 beats per minute. By inhibiting slow-current calcium channels, verapamil increased the refractoriness of the AV node and resulted in a decrease in the ventricular response rate in these patients. Atrial flutter with an average ventricular rate of 150 beats per minute was present in an additional eight patients. After treatment with verapamil, conversion to normal sinus rhythm occurred in seven patients, and in the eighth patient, a reduction in ventricular rate from 154 to 75 beats per minute occurred. Clearly, in the case of acute myocardial infarction, verapamil represents a significant therapeutic agent capable of rapidly reducing the ventricular response rate in patients with atrial fibrillation or atrial flutter. This effect could be beneficial in preserving ischemic myocardium or in relieving rate-related angina or heart failure. Hagemeijer's results require further investigation before verapamil can be recommended for treating acute myocardial infarction, but its potential usefulness cannot be ignored.

The Division of Cardiology at the University of California, San Francisco (UCSF) has used verapamil in the treatment of approximately 50 patients with supraventricular tachyarrhythmias. Our results using intravenous verapamil therapy have been similar to those of the studies outlined above; that is, approximately 85 percent to 90 percent had an excellent initial response.[11] In addition, long-term oral verapamil therapy has been evaluated in 18 patients followed for a mean of 16 months. Although verapamil produced objective and subjective improvement in the patients' supraventricular arrhythmias, 15 of the 18 patients required concomitant administration of either digoxin or another conventional antiarrhythmic drug to obtain the desired clinical response. The patients tolerated the on-going oral verapamil therapy without significant side effects, demonstrating that long-term treatment is both effective and nontoxic.

As with any drug, a clinician must weight the risk-benefit ratio before initiating treatment. Fortunately, verapamil has very low toxicity. A review of 8,072 patients treated with the drug, either intravenously or orally on a long-term basis, shows an overall incidence of side effects of 8 percent.[9] However, only 1 percent to 2 percent (73 patients) of the patients treated had to discontinue the drug because of intolerable side effects. The most common side effects (Table 4) were gastrointestinal, including nausea, vomiting and constipation.

Some patients, especially those predisposed to migraine, may have headaches. Whether these

TABLE 4.—*Common Side Effects of Verapamil and Amiodarone Therapy*

	Side Effects				
Drug	*Gastrointestinal*	*Central Nervous System*	*Integument*	*Endocrine*	*Cardiovascular*
Verapamil . .	Nausea Vomiting Constipation	Dizziness Vertigo Headache	Pruritis Rash Flushing	. . . . .	Bradycardia Hypotension Congestive heart failure AV dissociation or block
Amiodarone .	Nausea Constipation	Motor neuropathy Tremor Cerebellar ataxia	Corneal microdeposits Dermatitis Blueing of the skin	Hypothyroidism Hyperthyroidism	Bradycardia Hypotension AV nodal block

AV = atrioventricular

headaches are related to extracranial vascular smooth muscle relaxation is unknown.

Cardiovascular side effects are secondary to verapamil's effect on automaticity, conduction and contractility. Because it depresses phase 4 depolarization in the sinus node, verapamil can cause deterioration in sinus node function in patients with sick sinus syndrome. Because it decreases conduction through the AV node, verapamil can precipitate AV block. The negative inotropic properties of verapamil can result in congestive heart failure in patients with underlying left ventricular dysfunction, especially if given in conjunction with propranolol or disopyramide.

What does the future hold for verapamil as an antiarrhythmic agent? Once verapamil is approved by the Food and Drug Administration and clinical experience in the United States accumulates, verapamil will probably become the drug of choice for the short-term treatment of PSVT. It will probably become an adjunct to digoxin in controlling the ventricular response rate in patients with atrial fibrillation and atrial flutter, especially in patients with chronic lung disease. In addition, verapamil will be a useful adjunct in the long-term treatment of recurrent PSVT. At present, there are insufficient clinical data to support a role for verapamil in the treatment of ventricular tachycardia.

Encainide

In contrast to verapamil, encainide is an antiarrhythmic agent developed by the Mead Johnson Laboratories for specific use in the treatment of ventricular arrhythmias. Encainide is a unique agent, which combines the electrophysiological effects of lidocaine and quinidine (Tables 1 and 2).[12,13] At the cellular level, encainide shortens the duration of the action potential (an effect of lidocaine) and depresses the rate of rise of the action potential upstroke (an effect of quinidine); that is, encainide slows conduction in ventricular and His-Purkinje tissues. Encainide also increases the effective refractory period and decreases ventricular excitability (both effects of quinidine).

In contrast to quinidine, encainide has no consistent effect on the peripheral vasculature, and, hence, alterations in blood pressure are uncommon. The atrial muscle, AV node and sinus node are unaffected by the rapid administration of encainide intravenously.[12,13] However, the effects of long-term oral encainide treatment on these tissues have not been completely assessed. Thus, encainide combines the desirable ventricular antiarrhythmic characteristics of lidocaine and quinidine therapy without compounding unwanted side effects.

The clinical pharmacology of encainide is outlined in Table 3. The drug is rapidly absorbed after oral administration, is metabolized in the liver and has a half-life of approximately two hours. Despite its relatively short half-life, encainide can usually be administered every six hours. This is the result of the wide margin between drug plasma concentrations that suppress the arrhythmia and those that produce side effects. In addition, encainide may have active metabolites. Encainide does not produce significant changes in cardiovascular dynamics in normal volunteers.[14] To date, there is no comprehensive information available on the hemodynamic effects of encainide in patients with congestive heart failure.

Because encainide's development is recent, only a few clinical trials are available for review. Two of these, however, warrant in-depth analysis. Roden and colleagues[15] carried out studies in 11 patients without organic heart disease. The patients had no symptoms of angina, no conduction disturbances on the electrocardiogram and no evidence of heart failure (average ejection fraction by radionuclide ventriculography was 63 percent). The common denominator for the study group was a high frequency of ventricular arrhythmias. An average of 771 PVD's per hour were recorded during the placebo phase of the study. During encainide therapy, 10 of the 11 patients had virtually total suppression of PVD's; that is, the PVD frequency during drug therapy was 0.4 percent of the frequency during placebo. Hence, encainide was dramatically effective in suppressing premature ventricular depolarizations. The limitation of Roden's study is in its patient population. Clinicians are more interested in PVD suppression in patients with organic heart disease. It is in this group that complex PVD patterns may be harbingers of sudden death. Hence, total suppression of PVD's in these patients could lead to prevention of death from arrhythmias.

The evaluation of encainide in patients with organic heart disease is underway, and one clinical abstract is available for review. Mason and coworkers[16] evaluated encainide in 38 patients with recurrent ventricular tachycardia refractory to conventional medications. During the six months of follow-up, encainide prevented the clinical recurrence of ventricular tachycardia in 54 percent

of the treated patients. Although the short follow-up period precludes any definitive conclusions about the efficacy of encainide in this subgroup of patients, the initial results are encouraging.

At UCSF Medical Center, orally given encainide has been used for the treatment of high-frequency PVD's in patients with and without organic heart disease. Preliminary results are now available on the first 10 patients treated. During therapy, nine of the ten patients had virtually complete suppression of PVD's; the PVD frequency during therapy was less than 1 percent of the frequency during placebo. It appears, therefore, that encainide will be as effective in patients with organic heart disease as it has been in patients without such disease. The side effects of encainide have been limited for the most part to the central nervous system, with tinnitus, dizziness and headaches being observed in the reported series.

What is the future of encainide? If side effects remain minor, it may be very useful in suppressing symptomatic PVD's in patients with no organic heart disease. Encainide's role in treating patients with heart disease will require definition and will depend on the results of studies now in progress.

Tocainide

Tocainide, a primary amine analogue of lidocaine, was developed by the Astra Pharmaceutical Company. The addition of the amine side group enables tocainide to avoid the first pass degradation by the liver that orally administered lidocaine undergoes.[17] Basically, tocainide is an orally given lidocaine agent. The electrophysiological properties of tocainide are similar to those of lidocaine and are outlined in Tables 1 and 2.

Tocainide is rapidly and completely absorbed after oral administration. About 40 percent of the drug is excreted unchanged by the kidneys after a single dose, and the remainder is metabolized by the liver. The half-life of tocainide is six to eight hours and therapeutic drug levels in the blood range from 3 to 10 μg per ml. Five studies have evaluated the safety and efficacy of tocainide.[18-22] For the purpose of this review, the results of these studies have been combined. Investigators have noted a correlation between the response of arrhythmias to lidocaine and to orally administered tocainide. Patients responding to intravenous lidocaine therapy usually had a clinical response to orally given tocainide as well, whereas patients who did not respond to lidocaine did not respond to tocainide either. These studies evaluated 78 patients with coronary artery disease and chronic PVD's. After tocainide administration, 50 of the 78 patients had a reduction in PVD frequency of greater than 75 percent. This degree of suppression represented a significant reduction in PVD frequency. The literature also included data on 28 patients treated for symptomatic ventricular tachycardia with tocainide.[20,22] Many of these patients were in the acute phase of myocardial infarctions and, hence, represent a select subgroup of patients with recurrent ventricular tachycardia. When emergency treatment with tocainide was given either intravenously or orally, 15 of 28 patients had suppression of ventricular tachycardia. The follow-up interval of these patients varied from zero to ten months, and recurrences of arrhythmias were infrequent. The obvious limitations of these reports were the small number of patients studied, the limited follow-up and the uncontrolled selection of patients.

One of the main problems with tocainide treatment relates to the drug's side effects. In the clinical series reviewed, 57 percent of patients had minor side effects, which consisted of neurological complaints of tremor, headache, paresthesias, hot flashes or dizziness. Gastrointestinal upset was also frequent. Approximately 10 percent to 15 percent of the treated patients had to discontinue the drug because of intolerable side effects.

What is the future role of tocainide as an antiarrhythmic agent? Tocainide is effective in suppressing PVD's in those patients responsive to intravenous lidocaine therapy. However, treatment will be complicated by a high incidence of side effects, although it may be useful for patients refractory to conventional medications.

Amiodarone

Amiodarone is a benzofuran derivative available in Europe and South America. Although amiodarone will remain an experimental antiarrhythmic agent in the United States long after verapamil, encainide and tocainide are released, it warrants discussion because of its wide use in many referral centers. For example, it is the most commonly used experimental antiarrhythmic drug at the UCSF Medical Center.

The basic electrophysiology of amiodarone is unique because its primary effect is to prolong the transmembrane action potential duration (see Tables 1 and 2).[17] Amiodarone also produces a slight decrease in action potential upstroke velocity without changing automaticity. The clini-

cal electrophysiology of amiodarone consists of a prolongation of the atrial, AV nodal and ventricular refractory periods. In addition, amiodarone prolongs the refractory period of accessory AV pathways (such as Kent bundles and Mahaim fibers).[23] Amiodarone can drastically alter the surface electrocardiogram by producing prolongation of the PR, QRS and QT intervals.

Despite being used clinically for more than 15 years in Europe, little is known about the clinical pharmacology of amiodarone. The drug is 50 percent absorbed after oral administration and is eliminated by unknown mechanisms. A month after discontinuation of long-term amiodarone therapy, tissue levels of the drug have decreased by only 30 percent. Therefore, the half-life of amiodarone is not measured in hours or days but, literally, in weeks. Thus, weeks may be required to attain the desired clinical effect or to eliminate the drug after its discontinuation.

In addition to its antiarrhythmic properties, amiodarone has other physiological effects. It is a noncompetitive antagonist of both α- and β-adrenergic receptors.[17] Amiodarone's antianginal properties are probably related to this β-blocking effect. Despite blocking β-receptors, amiodarone does not usually result in depressed left ventricular function. This seeming paradox is explained by the drug's effect on the peripheral vasculature. Because it antagonizes α-receptors, amiodarone produces a decrease in systemic vascular resistance and reduces left ventricular afterload, thus balancing its β-blocking properties.

The literature contains several studies which evaluate the effectiveness of amiodarone as an antiarrhythmic agent. The largest series was reported by Rosenbaum and co-workers,[24] in which 252 patients with cardiac arrhythmias were studied. Because amiodarone exerts electrophysiological effects in atrial, ventricular and AV nodal tissue, the drug was used to treat a variety of arrhythmic conditions. Rosenbaum studied 30 patients with recurrent atrial fibrillation, atrial flutter, or both. The results of treatment were evaluated using *total* suppression of the arrhythmia as a positive response. During an average follow-up period of 16 months, 29 of 30 patients (97 percent) had a positive response to amiodarone therapy. Rosenbaum administered amiodarone to 59 patients with PSVT and reported that 54 patients (97 percent) had complete suppression of the tachycardia. A third subgroup investigated consisted of 44 patients with recurrent ventricular tachycardia refractory to conventional drugs. Amiodarone resulted in suppression of clinical ventricular tachycardia in 32 of the 44 patients (77 percent). These published results of amiodarone's excellent effectiveness have been substantiated in several smaller series.

At the UCSF Medical Center, amiodarone has been used in the management of both supraventricular and ventricular arrhythmias. The results in patients with atrial fibrillation and PSVT are similar to those reported by Rosenbaum and coworkers.[24] The largest group of patients treated at the medical center has had recurrent ventricular tachycardia, refractory to treatment with conventional drugs. Of 30 such patients treated with amiodarone, 9 patients had a clinical recurrence of ventricular tachycardia during therapy while 21 patients remained asymptomatic. The clinical suppression of ventricular tachycardia in 70 percent of the patients in this high-risk subgroup has been an encouraging finding.

Because amiodarone can be administered once daily, can be taken by patients with depressed left ventricular function, and is therapeutically effective, it would appear to have many characteristics of the ideal antiarrhythmic drug. However, amiodarone treatment can be accompanied by significant side effects (Table 4). For example, in most patients corneal microdeposits will eventually develop during treatment. These microdeposits do not usually interfere with vision and resolve when the patient discontinues the drug. The accumulation of deposits may be alleviated by the frequent use of methycellulose eye drops. Because the amiodarone molecule is 37 percent iodine by weight, thyroid dysfunction can occur. In approximately 1 percent to 3 percent of patients either hyperthyroidism or hypothyroidism will develop. Other side effects include photodermatitis, blueing of the skin when exposed to sunlight, various neurological abnormalities including motor neuropathy, and cerebellar ataxia. In general, the reported side effects of amiodarone resolve when the drug is discontinued.

Amiodarone is an effective multipurpose antiarrhythmic drug that is accompanied by frequent side effects which limit its use to arrhythmias that are refractory to conventional drug treatment.

Electrophysiological Techniques

The newer antiarrhythmic drugs are an important advance in the management of many types of refractory arrhythmias; however, complemen-

tary developments have occurred in the field of invasive electrophysiology as well. Although a comprehensive review is beyond the scope of this report, certain points are relevant to patients with ventricular arrhythmias. First, several investigators have shown that in patients with recurrent ventricular tachycardia, the clinical tachycardia can be reliably reproduced by electrical stimulation of the right ventricle without significant morbidity or mortality.[25,26] In addition, several studies have shown that failure in the cardiac catheterization laboratory to stimulate the tachycardia after drug administration is predictive of suppression of the arrhythmia during long-term therapy.[25,27] Thus, physicians now have a realtively safe and rapid means by which to assess the efficacy of antiarrhythmic therapy in patients with life-threatening ventricular arrhythmias. At present, these invasive techniques are used at the UCSF Medical Center to evaluate therapy in all patients with sustained ventricular tachycardia or aborted sudden death syndrome.

Conclusion

There will soon be available many newer antiarrhythmic drugs, each with its own advantages and side effects. Use of these drugs should be governed by a careful assessment of each drug's risk-benefit ratio for a particular patient. In this way, the care and quality-of-life of patients with arrhythmias can be much improved.

REFERENCES

1. Liberthson RR, Nagel EL, Hirschman JC, et al: Prehospital ventricular defibrillation: Prognosis and follow-up care. N Engl J Med 291:317-321, 1974

2. Cobb LA, Baum RS, Alvarez H 3d, et al: Resuscitation from out-of-hospital ventricular fibrillation: 4 years follow-up. Circulation 52(6 Suppl 3):223-235, 1975

3. Schaffer WA, Cobb LA: Recurrent ventricular fibrillation and modes of death in survivors of out-of-hospital ventricular fibrillation. N Engl J Med 293:259-262, 1975

4. Ruberman W, Weinblatt E, Goldberg J, et al: Ventricular premature beats and mortality after myocardial infarction. N Engl J Med 297:750-757, 1977

5. Moss AJ, Davis HT, DeCamilla J, et al: Ventricular ectopic beats and their relation to sudden and non-sudden cardiac death after myocardial infarction. Circulation 60:998-1003, 1979

6. Singh BN, Ellradt G, Peter CT: Verapamil: A review of its pharmacological properties and therapeutic use. Drugs 15:169-197, 1978

7. Lewis BS, Mitha AS, Gostman MS: Immediate haemodynamic effects of verapamil. Cardiology 60:366-376, 1975

8. Singh BN, Phil D, Roche AH: Effect of intravenous verapamil on hemodynamics in patients with heart disease. Am Heart J 94:593-599, 1977

9. Verapamil clinical information. Investigator's Brochure. Knoll Pharmaceutical, Feb 1977

10. Hagemeijer F: Verapamil in the management of supraventricular tachyarrhythmias occurring after a recent myocardial infarction. Circulation 57:751-755, 1978

11. Gonzalez R, Sheinman MM: Treatment of supraventricular arrhythmias with intravenous and oral verapamil. Chest, 1981 (In press)

12. Sami M, Mason JW, On G, et al: Canine electrophysiology of encainide, a new antiarrhythmic drug. Am J Cardiol 43:1149-1154, 1979

13. Sami M, Mason JW, Peters F, et al: Clinical electrophysiologic effects of encainide, a newly developed antiarrhythmic agent. Am J Cardiol 44:526-532, 1979

14. Roden DM, Reele SB, Oates JA, et al: Clinical significance of the ECG interval prolongation accompanying effective encainide therapy (Abstract). Am J Cardiol 45:473, 1980

15. Roden DM, Reele SB, Higgins SB, et al: Total suppression of ventricular arrhythmias by encainide. N Engl J Med 302:877-882, 1980

16. Mason JW, Peters FA: Antiarrhythmic efficacy of encainide in patients with refractory recurrent ventricular tachycardia (Abstract). Circulation 62(Suppl 4):153, 1980

17. Zipes DP, Troup PJ: New antiarrhythmic agents. Am J Cardiol 41:1005-1024, 1978

18. Winkle RA, Meffin PJ, Fitzgerald JW, et al: Clinical efficacy and pharmacokinetics of a new orally effective antiarrhythmic, tocainide. Circulation 54:884-889, 1976

19. Woosley RL, McDevitt DG, Nies AS, et al: Suppression of ventricular ectopic depolarizations by tocainide. Circulation 56: 980-985, 1977

20. Winkle RA, Meffin PJ, Harrison DC: Long-term tocainide therapy for ventricular arrhythmias. Circulation 57:1008-1016, 1978

21. Engler R, Ryan W, LeWinter M, et al: Assessment of long-term antiarrhythmic therapy: Studies on the long-term efficacy and toxicity of tocainide. Am J Cardiol 43:612-618, 1979

22. Ryan WB, Engler R, LeWinter M, et al: Efficacy of a new oral agent (tocainide) in the acute treatment of refractory ventricular arrhythmias. Am J Card 43:285-291, 1979

23. Wellens HJJ, Lie KI, Bar FW, et al: Effect of amiodarone in the Wolff-Parkinson-White syndrome. Am J Cardiol 38:189-194, 1976

24. Rosenbaum MB, Chiale PA, Halpern MS, et al: Clinical efficacy of amiodarone as an antiarrhythmic agent. Am J Cardiol 38:934-944, 1976

25. Horowitz LN, Josephson ME, Farshidi A, et al: Recurrent sustained ventricular tachycardia—3. Role of the electrophysiologic study in selection of antiarrhythmic regimens. Circulation 58: 986-997, 1978

26. Mason JW, Winkle RA: Electrode-catheter arrhythmia induction in the selection and assessment of antiarrhythmic drug therapy for recurrent ventricular tachycardia. Circulation 58: 971-985, 1978

27. Ruskin JN, DiMarco JP, Garan H: Out-of-hospital cardiac arrest: Electrophysiologic observations and selection of long-term antiarrhythmic therapy. N Engl J Med 303:607-613, 1980

Important Advances in Clinical Medicine

Epitomes of Progress—Urology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in urology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in urology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Urology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Diagnostic Fine-Needle Aspiration

FINE-NEEDLE ASPIRATION is a simple and safe method of great benefit in diagnosing malignant lesions. In most circumstances, 5-ml plastic Luer Lock syringes, 20-gauge needles and fixative solution are the only equipment needed.

Fine-needle aspiration can assist in diagnosing cancer in such diverse organs as the thyroid, breast and prostate, with minimal discomfort to the patient, and such a preoperative diagnosis greatly facilitates discussion regarding any planned ablative procedure. However, the technique has not yet advanced to the point where it can totally replace open or cutting-needle biopsy.

Aspiration biopsy is useful in the diagnosis and follow-up of secondary cancer as well. The malignant character of superficial lesions such as skin nodules or subcutaneous lymph nodes can be established without resort to incisional or excisional biopsy. Not only are the hazards of such procedures avoided but, because removal offers no therapeutic benefit, the lesion can be left in situ and used as a precise marker to follow the patient's response to treatment. Deep-seated masses which might otherwise require laparotomy are amenable to percutaneous needling, which is sometimes guided by fluoroscopy, ultrasound or computed tomography control.

Diagnosis depends on the evaluation of small pieces of tissue or individual cells and, thus, requires a skilled cytologist. It is emphasized that a positive result is highly significant. Negative findings on aspiration, due frequently to technical factors, are not helpful unless clear fluid is obtained, indicating the presence of a benign cystic disorder.

JEFFREY J. POLLEN, MD

REFERENCES

Kline TS, Neal HS: Needle aspiration biopsy: A critical appraisal—Eight years and 3,267 specimens later. JAMA 239:36-39, Jan 2, 1978

Pollen JJ, Schmidt JD: Diagnostic fine needle aspiration of soft tissue metastases from cancer of the prostate. J Urol 121: 59-61, Jan 1979

Ultrasonography in Evaluation of the Scrotum

EXAMINATION of the scrotum when underlying inflammatory, neoplastic or traumatic conditions are involved can be a difficult task. Frequently the presence of fluid, blood or inflammatory reaction surrounding the testes, as well as the patient's

sensitivity to examination, can hamper accurate physical examination of the scrotum and its contents.

Development of a "small parts" high-resolution ultrasound scanning apparatus for examining the scrotum has facilitated the diagnosis of pathological conditions. By placing the scrotum against the water bath of the scanning apparatus the operator can obtain an ultrasonic picture in a rapid, painless, harmless and noninvasive manner. While standard ultrasonography of the scrotum can resolve structures of approximately 1 cm, high-resolution machines have the capability to resolve structures as small as 3 mm. The addition of a "real time" element to these machines also makes it possible for the operator to obtain a dynamic picture of the contents of the scrotum.

At the University of California, San Diego, 22 patients were referred for evaluation of possible intrascrotal pathological conditions. These were characterized as follows: intratesticular masses in seven cases, extratesticular masses in two cases, extratesticular fluid of hydrocele or spermatocele origin in three cases and inflammations involving the epididymis and spermatic cord in eight cases; two patients were found to have normal testes. Of the seven patients considered to have intratesticular masses based on ultrasonographic findings, five were found to have a testicular tumor at surgical exploration.

While the small parts ultrasound scanner is useful in differentiating intratesticular from extratesticular pathology, it is not very helpful in the diagnosis of testicular or spermatic cord torsion. In this case, the Doppler ultrasonic stethoscope (used in detecting peripheral vascular blood flow) combined with clinical examination has given better diagnostic results.

DANIEL A. NACHTSHEIM, MD

REFERENCES

Gottesman JE, Sample WF, Skinner DG, et al: Diagnostic ultrasound in the evaluation of scrotal masses. J Urol 118:601-603, Oct 1977

Leopold GR, Woo VL, Scheible FW, et al: High-resolution ultrasonography of scrotal pathology. Radiology 131:719-722, Jun 1979

Detection of Nonpalpable Varicoceles

RECENT EVIDENCE has suggested that the deleterious effect of varicoceles on spermatogenesis is progressive. Therefore, early detection and surgical repair of this condition in a patient for whom a "varicocele effect" in semen analysis has been found are especially important should the man wish to remain fertile. Once the sperm count has fallen below 10 million sperm per ml, results of repair are poor compared with those when the count is over 20 million sperm per ml. Consequently, any man 20 years old or older for whom fertility has not been confirmed probably should have a semen analysis and, if it is abnormal, should be referred for treatment.

For those who have no palpable varicosity but do have a semen analysis consistent with varicocele, a physician can use the Doppler stethoscope to detect a nonpalpable varicocele instead of recommending "blind" spermatic vein ligation. A venous pulse can be detected in patients with varicoceles during a Valsalva maneuver because the valves in the spermatic vein are incompetent, allowing a retrograde flow of blood. Both the left and the right sides of the scrotum should be examined because the incidence of bilateral varicoceles is 16 percent or higher and both sides require repair to correct the problem. Again, the Doppler stethoscope can help determine which patients have nonpalpable varicoceles.

C. LOWELL PARSONS, MD

REFERENCES

Amelar RD, Dubin L, Walsh PC: Male Infertility. Philadelphia, WB Saunders Co, 1977

Greenberg SH, Lipshultz LI, Wein AJ: A preliminary report of 'subclinical varicocele': Diagnosis by Doppler ultrasonic stethoscope—Examination and initial results of surgical therapy. J Reprod Med 22:77-81, Feb 1979

Lipshultz LI, Corriere JN Jr: Progressive testicular atrophy in the varicocele patient. J Urol 117:175-176, Feb 1977

Oxalate Stone Disease After Jejunoileal Bypass Operations

FORMATION of oxalate stones in the urinary tract has been recognized recently as a complication of jejunoileal bypass operations for morbid obesity. Hyperoxaluria observed in a substantial majority of these patients constitutes the main initial factor in the pathogenesis of oxalate calculi.

By experimenting with oxalate labeled with carbon 14, Chadwick, Modha and Dowling established that increased absorption of exogenous oxalates was the cause of such hyperoxaluria. Subsequently, Dobbins and Binder observed that the enhanced absorption occurred in the colon as a result of increased mucosal permeability caused by excess bile and fatty acids. Steatorrhea, causing loss of calcium by saponification, prevents calcium-oxalate binding and, thereby, increases the soluble oxalate pool and, probably, contributes to easier absorption of oxalates. However, although

hyperoxaluria develops postoperatively in many patients, urinary calculi develop in only a small fraction of them. Gregory and associates failed to notice any significant difference in the incidence and degree of hyperoxaluria and hyperoxalemia between those in whom stones formed and those in whom they did not. Stone formers, however, showed a higher crystallization rate; also, the crystals that formed in their urine were larger. This indicates that the ultimate precipitation of oxalate crystals in patients with hyperoxaluria is determined by the presence or absence of certain yet undetermined factors.

At present, the prophylactic management of these patients includes (1) careful follow-up studies of urinary oxalate levels, (2) dietary restriction of oxalates and fats and (3) administration of oxalate-binding agents like cholestyramine or diethylaminoethanol cellulose. Calcium also binds oxalate in the gut, and most workers have found it effective in substantially reducing urinary oxalates. Gregory, however, has cautioned against the use of calcium salts based on his observation of an enhanced rate of urinary crystallization in animals given calcium orally following jejunoileal bypass operations.

SAKTI DAS, MD

REFERENCES

Clayman RV, Williams RD: Oxalate urolithiasis following jejunoileal bypass: Mechanism and management. Surg Clin North Am 59:1071-1077, Dec 1979

Dobbins JW, Binder HJ: Importance of the colon in enteric hyperoxaluria. N Engl J Med 296:298-301, Feb 10, 1977

Gregory JG, Park KY, Schoenberg HW: Oxalate stone disease after intestinal resection. J Urol 117:631-634, May 1977

Electron Microscopy for Detecting Changes in Undescended Testes

THE TIMING OF orchiopexy for boys with cryptorchidism has gradually changed over the past half century. Originally, postpuberty had been selected, but studies of spermatogenesis then suggested that the preschool years might be optimal. Recently, electron microscopy of undescended testes has cast doubt on that recommendation as well. Under electron microscopy, the spermatogonia of both cryptorchid and control testes appear the same during the first year of life. Thereafter, however, the density of the spermatogonia is decreased in a cryptorchid testis as compared with its control. Additionally, Leydig cells in an undescended testis appear to be damaged after the second year of life, while those of control testes do not. This information suggests that the optimal age for orchiopexy should be revised downward again to the second year of life. It has been shown that orchiopexy by a skilled physician can be accomplished as effectively in boys at 1 to 2 years of age as at a later age.

GEORGE W. KAPLAN, MD

REFERENCES

Hadziselimovic F, Kruslin E: The role of the epididymis in descensus testis and the topographical relationship between the testis and epididymis from the sixth month of pregnancy until immediately after birth. Anat Embryol 155:191-196, Jan 30, 1979

Scorer CG, Farrington GH: Congenital Deformities of the Testis and Epididymis. London, Butterworth, 1971

Antegrade Pyelography and Percutaneous Nephrostomy

ALTHOUGH antegrade pyelography and percutaneous nephrostomy are not new procedures, recent technical refinements have allowed their incorporation into the evaluation and treatment of patients with upper urinary tract disturbances. However, modern equipment and an experienced urologist or uroradiologist are required for their use.

Antegrade pyelography is essentially a diagnostic technique for evaluating ureteral transport and hydroureteronephrosis. Under fluoroscopic or ultrasound guidance and using local anesthesia, a special catheter is placed percutaneously into the dilated pyelocalyceal system. Urine is withdrawn for analysis, including culture and cytological studies. A contrast medium is then injected to fill out the collecting system after the patient has been repositioned for optimal delineation of the upper urinary tract. Continuous perfusion studies measuring pressure changes can be carried out in both children and adults in an attempt to distinguish true obstruction from simple dilatation of the collecting system (Whitaker test). A general anesthetic is usually given when carrying out the test in infants and children.

With percutaneous nephrostomy, a small firm catheter is left indwelling in the obstructed pyelocalyceal system for drainage of urine in conditions such as pyonephrosis or uninfected hydronephrosis. Also, patients with azotemia and other complicating factors can have rapid relief of ureteral obstruction without undergoing a general anesthetic, formal surgical nephrostomy or attempted cystoscopic manipulation and insertion of ureteral catheters. Bilateral percutaneous nephrostomy tubes can be inserted during the procedure if necessary. Recently, this technique has been modified for the manipulation and extraction of urinary tract calculi as well as for the antegrade stenting of strictures at the ureterovesical and ureterointestinal junctions. When renal function

has improved and infection is controlled, then permanent or definitive measures can be planned and carried out electively and more safely.

JOSEPH D. SCHMIDT, MD

REFERENCES

Smith AD, Lange PH, Miller RP, et al: Introduction of the Gibbons ureteral stent facilitated by antecedent percutaneous nephrostomy. J Urol 120:543-544, Nov 1978

Link D, Leff RG, Hildel J, et al: The use of percutaneous nephrostomy in 42 patients. J Urol 122:9-10, Jul 1979

Ho PC, Talner LB, Parsons CL, et al: Percutaneous nephrostomy: Experience in 107 kidneys. Urology 15:532-535, Dec 1980

Serum Markers for Detecting Testicular Tumors

RADIOIMMUNOASSAY has made possible the accurate measurement of serum α-fetoprotein (α-FP) and β-human chorionic gonadotropin (β-HCG). These serum markers are elevated in a significant number of patients having testicular tumors originating from germ cells. When used together, these markers have been found to be elevated in 70 percent to 94 percent of patients with nonseminomatous germ cell tumors, such as embryonal cell carcinoma, teratocarcinoma and choriocarcinoma. With pure seminoma, the most radiosensitive of the testicular tumors, elevation of β-HCG has been noted in 5 percent to 10 percent of cases. The source of this elevation is thought to be syncytiotrophoblastic giant cells interspersed in the seminoma. The detection of an elevated α-FP in what is thought to be pure seminoma, however, indicates the need for a further search for other tumor elements.

α-FP is a glycoprotein produced by fetal yolk sac, liver and some gastrointestinal tract cells. It is present in the human fetus and reaches low levels (less than 40 ng per ml) by 1 year of age. In addition to elevated levels in patients with testicular embryonal cell carcinoma and teratocarcinoma, α-FP elevations have been noted in patients with hepatocellular, pancreatic, gastric and colonic carcinoma as well as those with Laennec cirrhosis.

Human chorionic gonadotropin, a glycoprotein composed of an α and β chain, is normally secreted by the placenta. Germ cell tumors of the testis often contain specialized cells capable of HCG production. Earlier methods were able to detect HCG in only 20 percent to 30 percent of nonseminomatous tumors whereas a 40 percent to 60 percent detection rate is now possible for β-HCG, based on a technique using an antibody to the β chain.

Clinically, these tumor markers have aided in the preoperative evaluation of testicular masses; for example, elevated values are strong evidence of a neoplasm. While the half-life of α-FP is approximately five days and that of β-HCG is 16 hours, a waiting period of two to three weeks following orchiectomy is advised before these tests are repeated. Persistent elevation of these serum markers indicates residual disease in a patient following orchiectomy. Also, reappearance of elevated markers that had previously returned to normal levels generally indicates recurrence of the disease. The larger the tumor burden, the more likely the elevation in the level of serum markers.

Perhaps the most valuable use of these tumor markers is in detecting residual or recurring tumors in patients with nonseminomatous germ cell tumors who have had stage I (confined to the testis) or stage II (tumor present in retroperitoneal lymph nodes) disease. In addition, in patients with stage III disease (advanced metastasis), response to radiation or chemotherapy can be monitored by checking the serum levels of these marker proteins.

DANIEL A. NACHTSHEIM, MD

REFERENCES

Fowler JE Jr, Taylor G, Blom J, et al: Experience with serum alpha-fetoprotein and human chorionic gonadotropin in nonseminomatous testicular tumors. J Urol 124:365-368, Sep 1980

Lange PH, Fraley EE: Serum alpha-fetoprotein and human chorionic gonadotropin in the treatment of patients with testicular tumors. Urol Clin North Am 4:393-406, Oct 1977

Scardino PT, Cox HD, Waldmann TA, et al: The value of serum tumor markers in the staging and prognosis of germ cell tumors of the testis. J Urol 118:994-999, Dec 1977

Immediate Versus Delayed Endocrine Therapy for Prostatic Carcinoma

IN 1941 Huggins and Hodges reported the almost miraculous response of cases of far advanced prostatic carcinoma to treatment with diethylstilbestrol (DES). Following this report endocrine manipulation became the accepted treatment for patients with prostatic carcinoma. Treatment involved DES therapy, an orchiectomy, or both, and was started as soon as the diagnosis was made. In 1967 the Veterans Administration Cooperative Urological Research Group reported that patients with early prostatic carcinoma (stages I and II) who were given DES had a shorter survival time than those given a placebo and suggested that endocrine manipulation be withheld until the severity of symptoms necessitated relief.

Our retrospective study agrees with their conclusions. The 15-year survival rate of patients with stage I and II lesions was 24 percent (23 of 95)

for those receiving therapy when the diagnosis was first made and 32 percent (16 of 50) for those receiving therapy when symptoms were noted.

However, the survival rate of patients with far advanced prostatic carcinoma (stages III and IV), who were seen between 1927 and 1941 and who had had endocrine manipulation after 1941, was 62 percent at five years and 31 percent at ten years. The survival rate was only 23 percent at five years and 0 percent at ten years for patients who had not received endocrine therapy.

Therefore, there is evidence that endocrine therapy for patients with prostatic carcinoma should be given only when symptoms from the extension of the neoplasm develop. Approximately 80 percent of patients will respond to treatment at this time.

Bilateral orchiectomy is usually preferable to DES therapy because of the following: (1) there is no aggravation of cardiovascular disease, (2) there are fewer feminizing changes and (3) treatment is usually more effective and longer lasting. In addition, leaving the epididymis intact when orchiectomy is done causes less psychological trauma than removing the entire contents of the scrotum.

ROGER BARNES, MD
HENRY HADLEY, MD
R. T. BERGMAN, MD

REFERENCES

Barnes R, Hadley H, Axford P, et al: Conservative treatment of early carcinoma of prostate: Comparison of patients less than seventy with those over seventy years of age. Urology 14:359-362, Oct 1979

Klein LA: Prostatic carcinoma. N Engl J Med 300:824-833, Apr 12, 1979

Abdominal Staging Methods for Study of Testicular Tumors

RECENT ADVANCES in the study of testicular tumors include the discovery of reliable serum markers and the development of effective chemotherapy. These advances are causing renewed interest in nonsurgical staging methods and a reassessment of recommendations for treatment of low-stage, nonseminomatous germ cell testicular tumors. Because nonoperative abdominal staging methods are inadequate, the ability of abdominal ultrasonography (US) and computed tomography (CT) to predict retroperitoneal metastasis was studied in 36 patients with testicular tumors.

CT was completed in 32 patients and US in 21 within a month before surgical removal and pathological examination of retroperitoneal lymph nodes. The pathological diagnosis was correctly predicted by CT in 28 of the 32 patients (87 percent) and by US in 17 of the 21 patients (81 percent). By both modalities, the three false-positive diagnoses were for patients with minimally enlarged nodes and the false-negative diagnosis was for a patient with microscopic tumor. Comparison by pathological staging showed that stage I disease was predicted correctly by CT in 13 of 16 patients (81 percent) and by US in 4 of 6 patients (67 percent). In stage II disease, 12 of 13 cases (92 percent) were correctly predicted by CT and 11 of 12 cases (92 percent) by US. In stage III disease diagnosis by both US and CT was correct in all three patients. The sensitivity (accuracy in detecting tumorous nodes) of both CT and US was 93 percent. However, the specificity (accuracy in detecting tumor-free nodes) was 82 percent by CT and 57 percent by US.

It was concluded that both US and CT are reliable techniques for pretreatment assessment of the status of retroperitoneal lymph nodes in patients with nonseminomatous germ cell testicular tumors. Of the two methods, CT is slightly more accurate, definitely more specific and, when available, is the recommended study. Inasmuch as neither US nor CT is capable of detecting microscopic disease, retroperitoneal lymphadenectomy continues to be the most reliable staging technique.

RICHARD D. WILLIAMS, MD

REFERENCES

Williams RD, Feinberg SB, Knight LC, et al: Abdominal staging of testicular tumors using ultrasonography and computed tomography. J Urol 123:872-875, Jun 1980

Ferrucci JT Jr: Body ultrasonography (second of two parts). N Engl J Med 300:590-602, Mar 15, 1979

Fraley EE, Lange PH, Kennedy BJ: Germ-cell testicular cancer in adults. N Engl J Med 301:1370-1377, 1420-1426, Dec 20, 1979 and Dec 27, 1979

Detection of Specific Prostatic Acid Phosphatase

CONVENTIONAL METHODS for the detection of elevated levels of serum acid phosphatase in patients with prostatic cancer have used a variety of enzyme substrates and inhibitors of the prostatic fraction of acid phosphatase. This indirect measurement of the prostatic contribution to acid phosphatase activity is subject to error and variation because of the many isoenzymes of acid phosphatase present in serum.

Newer immunologic techniques have produced antibody to prostatic acid phosphatase (PAP) itself and have made possible more specific, sen-

sitive and stable measurements of this important marker of prostatic cancer.

Now commercially available, the two main methods are a radioimmunoassay (RIA-PAP), which is measured in ng per ml, and a semiquantitative counterimmunoelectrophoresis (CIEP-PAP), measured by the density of precipitate formed on electrophoresis. CIEP-PAP is relatively simple, rapid and inexpensive but suffers greatly from a lack of quantitation in its present form. RIA-PAP, while technically more difficult, time-consuming and expensive, is reproducible and highly quantitative.

Early experience with these two methods has resulted in detection of abnormal levels of specific PAP in up to 50 percent of patients with prostatic cancer confined to the gland (when it is more easily cured and the possibility of surgical removal exists) when using RIA-PAP and 30 percent when using CIEP-PAP. Unfortunately, most cases of prostatic cancer are diagnosed in the advanced stages. At this point, immunologic detection of elevated levels of acid phosphatase reaches 80 percent to 90 percent.

Although rare instances of false-positives have been reported—for example, with carcinoma of the pancreas, these immunologic methods appear specific enough to exclude the prostate as the cause of spurious acid phosphatase elevations when measured by the standard enzymatic methods.

Great enthusiasm accompanied the availability of the RIA-PAP test for the detection of undiagnosed carcinoma of the prostate and, to a limited extent, this has been justified. Its usefulness in massive random screening, however, has not been justified in theory or in practice. Early investigators have indicated that the advantage of using the RIA-PAP measurement lies in its ability (1) to measure the enzyme accurately despite conditions (such as time and temperature) to which the specimen is subjected before it is analyzed (stability) and (2) to establish a normal value for a particular patient, so that elevations in subsequent tests may indicate a pathological condition even though the test results may lie within the normal range (sensitivity).

DANIEL A. NACHTSHEIM, MD

REFERENCES

Foti AG, Cooper JF, Herschman H: Counterimmunoelectrophoresis in determination of prostatic acid phosphatase in human serum. Clin Chem 24:140-142, Jan 1978

Griffiths JC: Prostate-specific acid phosphatase: Re-evaluation of radioimmunoassay in diagnosing prostatic disease. Clin Chem 26:433-436, Mar 1980

Murphy GP, Karr J, Chu TM: Prostatic acid phosphatase: Where are we? CA 28:258-264, Sep/Oct 1978

Watson RA, Tang DB: The predictive value of prostatic acid phosphatase as a screening test for prostatic cancer. N Engl J Med 303:497-499, Aug 28, 1980

ADVISORY PANEL TO THE SECTION ON UROLOGY

STANLEY BROSMAN, MD
Advisory Panel Chairman
Section Editor
CMA Scientific Board Representative
Santa Monica

RODERICK TURNER, MD
CMA Section Chairman
Los Angeles

JOHN J. SUMMERS, MD
CMA Section Secretary
Los Angeles

DAVID W. FERGUSON, MD
CMA Section Assistant Secretary
Redding

HENRY L. HADLEY, MD
Loma Linda University

ROBERT KESSLER, MD
Stanford University

J. M. PALMER, MD
University of California, Davis

DONALD C. MARTIN, MD
University of California, Irvine

JOSEPH J. KAUFFMAN, MD
University of California, Los Angeles

JOSEPH D. SCHMIDT, MD
University of California, San Diego

EMIL TANAGHO, MD
University of California, San Francisco

DONALD SKINNER, MD
University of Southern California
Los Angeles

DUNCAN E. GOVAN, MD
Stanford University

LEE HARBACH, MD
San Diego

HERBERT SCHWARZ, MD
Santa Ana

EDITORIALS

Welcome NMMS

With this issue The Western Journal of Medicine welcomes a sixth state medical association into the family of this increasingly regional journal. In November 1980 the House of Delegates of the New Mexico Medical Society voted to adopt the WJM as its official journal and to have its members receive the journal as a benefit of their membership. The WJM serves the medical associations in California, Idaho, Nevada, Utah, Washington state and now New Mexico. The circulation, which now is about 45,000, also includes subscribers from every other state and from abroad.

The WJM seeks to be a truly useful journal for its readers, the greatest number of whom are practitioners. It seeks to offer a variety of fare which also includes something of interest for students, academicians, researchers and even political leaders of our profession—of whom there are many among its readers. It seeks to reflect the vitality and achievements in science, education and practice that are hallmarks of medicine in the West, and to give these a stronger presence in the medical literature. The editors, the editorial board and many others are dedicated to making this journal a regional instrument of physician education and continuing education in the West, and also an increasingly distinguished journal on the national scene.

We warmly welcome the New Mexico Medical Society to the WJM family of associations and its members to our readership. We look forward to a long and productive relationship which should be of genuine benefit to all concerned. —MSMW

Measuring Blood Pressure in Young Patients

Diseases come into medical prominence when they are seen to be urgent causes of death, when they present and are diagnosable as entities or syndromes that can be labeled (although not necessarily treated) or when an apparently effective therapy or cure appears. Hypertension and, concomitantly, the clinical measurement of blood pressure is no exception to this dictum.

In ancient times anyone seeing an arterial wound or a fallen comrade bleed to death had to observe that the blood spurted out, and the receptive mind must long ago have entertained the idea that the blood was under pressure in life. But it was not until Stephen Hales' experiments on hapless horses in 1733[1] that alterations in blood pressure with changes in physiologic states and changes from animal to animal were recognized and recorded. Hales' discovery had no effect on either the medical profession's understanding of blood pressure or its treatment of patients—nor did Poiseuilli's dissertation a century later, despite his report of the rise and fall of blood pressure with respiration in horses, essentially a repetition of Hales' work but using a mercury manometer.[2] His thesis did, however, mark the beginning of the research and development which was to lead, 70 years later, to the demonstration by Riva Rocci[3] that systolic blood pressure could be measured noninvasively in humans using a rubber bag in an inelastic cuff coupled to a rubber bulb and a mercury manometer.

While this auscultatory technique did simplify the equipment needed to measure blood pressure and eliminate the errors associated with dependence upon pulse obliteration, its description as an "instrument of precision devoid of intrinsic error"[4] now seems premature if not fulsome.[5,6] So, too, does the ready acceptance of "normal"—that is, unassociated with disease—values for systolic and diastolic pressure.[7]

Indeed this all too ready acceptance, based on too few data, may be the root cause of pediatricians' decreased interest during the middle decades of this century in taking and recording blood pressure as part of the routine examination of "normal" children. Few cases of hypertension by adult standards were found, and the recognition that idiopathic hypertensive cardiovascular disease is associated with an "undetermined period of unsuspected, unfelt, symptomless hypertension"[4] was

Also see the Medical Progress article "Blood Pressure in Infants, Children and Adolescents" by Arthur J. Moss, MD.

not appreciated as extending to the pediatric age group.

In adults the story was quite different. One did not need to record many pressure levels before becoming aware that severe hypertension was often followed by death from uremia or apoplexy; that "35 percent of the cases rejected for high tension alone later proved to have serious ailments which were good bases for rejection" (for life insurance),[4] and that a hypertensive crisis required urgent measures if the patient was to be saved. But these dramatic events obscured the more persistent and numerically more important problems of what we still call *essential* hypertension—which is to say that its cause or causes are essentially unknown.

Similarly, in the rush to incorporate Riva Rocci's apparatus into clinical practice (in 1930 Major wrote that it "has been practically universally employed for the past thirty years"[2]), the error of failing to feel the pulse at the same time that the systolic reading was being obtained became increasingly common. Unless this is done, severe hypertension may not be detected in the young—in whom the cuff is often inflated only to 150 mm of mercury and in whom an auscultatory gap is not uncommon. Conversely, the systolic pressure may be normal, as the pulse will indicate, while by auscultation it appears to be beyond 300 mm of mercury due to the violent sound made as the blood stream strikes the top of the inflated cuff in aortic insufficiency. Measurement difficulties attendant upon irregularities in rhythm can be readily resolved if the pulse is routinely felt as the blood pressure is taken but not if this practice is neglected.[8]

But these sins of omission were unimportant compared with the sins of commission that accompanied earlier, and later, attempts at therapy. In 1924 one of the recommended therapies was exposure to radium emanations "which are sometimes efficacious and will probably do no harm."[9] Other therapies were intramuscular injections of sulfur, repeated doses of bromides, and administration of strong tea and coffee.[9,10] Decreasing the intake of sodium, first proposed in 1922, has withstood the test of time better. We have still, however, to acquire exact knowledge, as Barker noted in 1922, "(a) of the internal and external causes that are operative in each form of hypertension, (b) of the effects that follow upon causative influences and (c) of the serial order in which those effects make their appearance."[9]

Perhaps if we had paid more attention to Barker's advice we would not now still be facing the twin dilemmas of whom we should screen for hypertension and why. Arthur Moss, in his review (elsewhere in this issue) of the need for, and problems in, measuring blood pressure in infants, children and adolescents, does a real service to medical practitioners in setting forth the whys and wherefores of this important clinical measure of health and disease. Data showing the distribution of blood pressures in youngsters are now available[11] from which determinations of "high blood pressure" can be individually made. The suggestion (in the Moss article) that a pressure of greater than 140/90 in patients older than 10 years of age, and 130/85 in children younger than 10 years, be considered as indicative of hypertension seems reasonable considering the current state of our knowledge.

I see no reason why $50 million need be spent, as North suggests,[12] and 4 million children labeled hypertensive simply because careful, routine blood pressure measurements should be a part of every child's regular physical examination. For years height and weight have been measured and charted with no excessive dollar outlay, no undue labeling of dwarfism, gigantism, obesity or cachexia. Indeed the grid charting of these measures of growth and development has proved most helpful in establishing a child's own pattern of body size and in indicating when that pattern is out of kilter. Plotting of blood pressure values on similar grids* could be equally useful. If done well, they could also provide the statistical normal values so dear to so many hearts.

Blood pressure values and height and weight should be considered together because blood pressure increases as the child grows and remains proportional to lean, as well as total, body mass.[13] Nor need one shy away because of the difficulty of calculating body mass; height alone is an excellent correlate with blood pressure.[14] Moreover, these correlates have been found to be constant among groups that genetically and socioculturally have, apparently, nothing in common.[11,13,15,16]

To be sure, as Moss quoted an American Heart Association committee,

> It is important to realize that even a one-time statement by a physician that a patient, whatever the patient's age may be, has "hypertension" can haunt a patient throughout a lifetime of job applications, life insurance rates, and social decisions such as choosing a vocation, decid-

*Blood Pressure Measurement Charts for Children. Available without charge from Mead Johnson Nutritional Division, 2404 W. Pennsylvania St., Evansville, IN 47721.

ing to marry, and determining when to seek advice for new signs and symptoms that may, or may not, be related to high blood pressure.

But to eschew routine measurements of blood pressure lest some physician erroneously label a patient hypertensive is akin to suggesting that temperature not be taken lest a patient be erroneously thought to have an infection and unnecessarily treated with an antibiotic. One hopes the medical profession has passed beyond knee-jerk diagnosis and therapy.

A word of caution is, perhaps, in order. *Tracking* has become an *in* word recently in the medical literature, and many articles purport to present data definitively clarifying this issue. Tracking is generally defined as the degree of consistency of peer rank order over time. But time, in this context, is decades, not years. Follow-up studies of two to five years yield little prognostic information about developing hypertension. What we need to know is whether or not persons track from infancy to childhood to adult life. Armed with these data we can begin to look for internal or external events or stimuli that precipitate a change of *track,* the development of hypertension or the moving away from an apparently high-risk *track*. Such data are available.[15] They are available because during the 1920's pediatricians interested in growth and development thought, unlike North and those who share his opinions, that blood pressure was worth measuring and was an important determination of growth and development. All that remains is for these data to be analyzed appropriately. One can only wonder why such analyses have not been seen as worth doing.

One other point remains to be considered; that is the prognostic significance of "labile" hypertension. What does one high reading of a child's blood pressure mean? Obviously some causes are readily found: anxiety, unusual exertion, particular surroundings, and so forth. But for a child in his normal surroundings, in a routine physical examination with a carefully taken pressure measurement, what does one incident of elevated pressure mean? Here, unfortunately, there are no data awaiting analyses to provide the answer. This does not make the question any less important.

This is a time when the diseases of aging are coming to the fore, when chronic diseases and, particularly, cardiovascular *degenerative* disorders are the single biggest cause of morbidity and mortality. It is imperative that, while taking good care of our young patients, we keep their whole life span in mind, beginning with a sensible watch for precursors of later disease during examinations. The disease state of hypertension is one of the easiest early warning signs to measure. Easy and inexpensive to obtain, a normal blood pressure reading is also a reassuring indicator of good health.

SHEILA C. MITCHELL, MD
Princeton, New Jersey

REFERENCES

1. Hales S: An account of some hydraulic and hydrostatical experiments made on the blood and blood vessels of animals, 1733, *In* Willius FA, Keys TE: Classics of Cardiology, Vol I. New York, Henry Schuman Inc & Dover Pub Inc, 1941, pp 127-155

2. Major RH: The history of taking of blood pressure. Ann Med Hist 2:47-55, 1930

3. Rocci R: Un nuovo sfigmomanometro. Gaz med di Torino 47:981-1001, 1896

4. Rice AG: The Value of Blood Pressure in the Diagnosis and Prognosis of Disease. Providence, Snow and Farnham Co, 1916, pp 6, 40, 51

5. Blumenthal S, Epps RP, Heavenrich R, et al: Report of the task force on blood pressure control in children. Pediatrics 59 (2 suppl):I-II, 797-820, May 1977

6. Blackshear PL Jr, Labarthe DR, Castle CH, et al: Report of the task force on automated blood pressure measuring devices for mass screening. DHEW publication No. (NIH) 76-929, US Dept of Health, Education, and Welfare, 1976

7. Mitchell SC, Blount SG, Blumenthal S, et al: The pediatrician and hypertension. Pediatrics 56:3-5, Jul 1975

8. Levine SA, Proctor HW: Clinical Auscultation of the Heart. Philadelphia, WB Saunders Co, 1950, pp 285-291

9. Barker LF: The treatment of so-called essential arterial hypertension. Read by invitation before the New York County Medical Society, Dec 22, 1924

10. Cecil RL, Loeb RF (Eds): Textbook of Medicine, 10th Ed. Philadelphia, WB Saunders Co, 1959, p 1196

11. Cardiovascular Profile of 15,000 Children of School Age in Three Communities, 1971-1975. DHEW publication No. (NIH) 78-1472. US Dept of Health, Education, and Welfare, 1978

12. North AF Jr: Is it worth $50 million? (Letter). Pediatrics 59:788-789, 1977

13. Voors AW, Webber LS, Frerichs RR, et al: Body height and body mass as determinants of basal blood pressure in children—The Bogalusa Heart Study. Am J Epidemiol 106:101-108, 1977

14. Roche AF, Eichorn E, McCammon RW, et al: The Natural History of Blood Pressure—Final Report on Contract No. 1-HV-42985 from the National Heart, Lung and Blood Institute. US Dept of Health, Education, and Welfare, National Institutes of Health, 1979

15. Makela M, Barton SA, Schull WJ, et al: The multinational Andean genetic and health program—IV. Altitude and the blood pressure of the Aymara. J Chronic Dis 31:587-603, 1978

16. Beaglehole R, Salmond SE, Eyles EF: A longitudinal study of blood pressure in Polynesian children. Am J Epidemiol 105: 87-89, 1977

Patients and Others as Doctors

THESE ARE TIMES of anti-intellectualism, antiprofessionalism and antielitism. An egalitarian mood prevails. In the current dialogue about concepts of health care, there seems to be a particular and somewhat pejorative focus on what many consider an overly authoritative or paternalistic stance by physicians and indeed by the medical profession as a whole. This has taken several forms. A growing number of persons now wish to know more about their own bodies and to make their own decisions about what will be done with

them. This trend is reflected, for instance, in attitudes toward abortion and in the legal doctrine of informed consent, which mandates that patients be fully informed and give their consent to whatever is done or not done in their cases. And, evidently not trusting physicians to inform their patients fully, at least one state has gone further and mandated in its Health and Safety Code that each woman with breast cancer must receive a state-approved brochure, describing in some detail the various approaches to effective management of her disease. In essence, the decision-making responsibility in patient care seems to be shifting away from attending physicians and is coming more and more to lie with patients themselves, with the help of others.

Besides government, as in the instance just cited, the *others* also include other health professionals who seek stronger and more independent decision-making authority for themselves in patient care. In a way it is paradoxical that the antielitism directed toward medicine by these others on the health team is being used by them as justification to press for a stronger, more elite and more independent professional status for themselves in patient care. Be this as it may, the trend today seems to be to look upon decision making in patient care more as an exercise in participatory democracy, in which the patient, the physician and other health care professionals involved are to confer on a more or less equal basis and collaboratively decide what should be done. For physicians it is worth noting that each incremental step in this process has the effect of lessening a physician's professional authority without necessarily lessening commensurately professional responsibility. The latter seems to remain relatively intact.

This egalitarian approach to patient care seems to infer that a physician has no more to contribute than have any of the other participants in the process. But is this true, and if not why not? In all fairness a collaborative approach might work well enough when the process can be carried out unhurriedly and in a relaxed atmosphere. But physicians know that in the real world urgency and tension are more likely to be the rule. Sickness, pain and fear are what frequently bring patients to a physician, and they come seeking authoritative help from a professional whom they believe has knowledge, sensitivity and skills which they hope and trust will help to overcome a problem they perceive as beyond their ability to handle by themselves. Physicians also know that patients who are ill, in pain or fearful are often simply not capable of understanding all of the pros and cons of their condition or of making sound decisions in their own behalf. And physicians are aware that while other health professionals have knowledge and skills that are useful and often essential for diagnosis and treatment, it is physicians who are best qualified to determine what is wrong, what is likely to happen and what can best be done about it. It is for reasons such as these that physician dominance in health care came into being and should not be lightly cast aside despite the current and apparently growing infatuation with an antielitist egalitarian approach.

A case in point is that of the late Dr. Franz J. Inglefinger who contracted an almost universally fatal disease about which he was an acknowledged, even world renowned authority. He discussed his experience frankly in an article recently published in the *New England Journal of Medicine*.[1] For many reasons this article is worth careful reading and careful pondering. In it Inglefinger points out that there could scarcely have been a better informed patient than he and that there was no lack of well-intentioned collaborative professional and other advice. But he states the "lack of authoritarian decision brought agony to me and my family," and that this was only relieved when he listened to the advice of a wise physician friend who said, "What you need is a doctor." Inglefinger then says the following:

> He was telling me to forget the information I was receiving from many quarters, and to seek instead a person who would dominate, who would tell me what to do, who would in a paternalistic manner assume responsibility for my care. When that excellent advice was followed, my family and I sensed immediate and immense relief.

This episode reflects reality and serves to put decision making in patient care into a truer perspective.

The pendulum is swinging pretty far toward acceptance of a belief that patients and others can substitute themselves for a trained and experienced physician in patient care. This is not to say that the views and participation of patients and others in diagnosis and treatment are not essential in the matrix of the decision process. But it is perilous to ignore the special role of a physician or to substitute the patient or the kinds of others that have been described in this role. There is a place and, usually, a need for the special knowledge, sensitivity and skills of a physician—

and, yes, for authoritative paternalism in medicine. The medical profession should be much more clearly heard in this important dialogue which is actively going on in the field of health care, and which is too often being carried on by persons who have never had a close personal contact with serious illness either as physicians or as patients.

—MSMW

REFERENCE

1. Ingelfinger FJ: Arrogance (Special Article). N Engl J Med 303:1507-1511, Dec 25, 1980

From Clubbing to Collagen

THE CASE REPORTS of idiopathic hypertrophic osteoarthropathy and retroperitoneal fibrosis in this issue offer an intriguing contrast in the pathogenesis and morbidity of two diseases associated with excessive connective tissue proliferation. The 72-year-old man with pachydermoperiostosis was largely asymptomatic with thickened skin of the lower extremities, acro-osteolysis and broadening of certain bones associated with periostitis. Many of the clinical features in cases of idiopathic hypertrophic osteoarthropathy, such as increased sweating, thickened skin and furrowed facies, resemble effects due to excessive growth hormone in acromegaly. The initial bony lesion is periosteal edema and elevation with a mild round cell infiltrate.

In contrast, in the 21-year-old Marine with retroperitoneal fibrosis there was systemic toxicity with symptoms including temperatures to 38.9°C (102°F), weight loss, anemia, myalgias and arthralgias. Retroperitoneal fibrosis as found at laparotomy is one stage in a disease that proceeds from an intense inflammatory reaction with lymphocytic infiltrates to dense fibrosis. Are the factors promoting collagen synthesis and the products synthesized in these diseases different? Is connective tissue synthesis associated with disease analogous to the immune response in that it may be modulated by factors such as the genotype and metabolic vagaries of the individual patient? For example, retroperitoneal fibrosis may be either idiopathic, as in this case, or induced by certain drugs such as methysergide, practolol or, rarely, propranolol.[1] Patients with retroperitoneal fibrosis frequently have other fibrotic diseases such as Dupuytren contractures, keloids, Peyronie disease or Riedel struma. More familiar diseases may also have similar associations. Dupuytren contractures occur more frequently in Laennec cirrhosis; biliary cirrhosis is associated with the CREST variant (CREST stands for calcinosis, Raynaud phenomenon, esophageal motility disorder, sclerodactyly and telangicetasia) of progressive systemic sclerosis. Perhaps these patients have an inherent tendency to respond to injury by exuberant connective tissue proliferation or to metabolize certain drugs differently. The answer to this problem is relevant not only to understanding the pathogenesis of the esoteric diseases discussed in these case reports, but, also, to understanding some of the principal causes of human morbidity such as alcoholic cirrhosis, in which the disease develops in only one of three who abuse alcohol.

A variety of agents stimulate connective tissue proliferation as measured by collagen synthesis in vitro. These include compounds associated with an acute or chronic inflammatory response such as serotonin and lymphokines. In addition, enhanced synthesis occurs with growth hormone as well as with less well-defined factors such as low molecular weight peptides found in experimental hepatic fibrosis, breast cancer with desmoplastic reaction and sera from patients with progressive systemic sclerosis.[2] Whether each has unique effects limited to specific organ systems and collagen types or whether each exerts its effect by a common mechanism such as induction of a second messenger is unknown. Currently, five collagens with different primary amino acid sequences are recognized. Types I and III are most relevant to this discussion because they occur in skin, tendons, scars and blood vessels. Bone contains only type I. Type II is found in cartilage, nucleus pulposus and vitreum. Type IV is the principal form in basement membranes and type V is associated with cell membranes in cartilage and many other tissues.

Preliminary evidence suggests that lymphokines and circulating soluble factors initiate a fibrotic reaction by stimulating a certain population of fibroblasts to proliferate and then produce collagen which is largely type I.[3] Newly synthesized collagen may be rapidly degraded by collagenase until it is incorporated into the extracellular fibril

Case reports entitled "Idiopathic Hypertrophic Osteoarthropathy (Pachydermoperiostosis)" and "Retroperitoneal Fibrosis as a Cause of Fever of Undetermined Origin" appear elsewhere in this issue.

and cross-linked. Cross-linked fibrils are much more resistant to collagenase.[4] Just as local production of rheumatoid factor by B lymphocytes in synovial tissue amplifies the inflammatory response, continued local production of lymphokines or exposure to serotonin or related compounds may magnify the effect on collagen synthesis in diseases such as retroperitoneal fibrosis. The type of collagen synthesized may affect the size of fibrils formed. This in turn would affect the rate of cross-linking and subsequent collagenolysis by collagenase and phagocytosis. For example, increased concentrations of calcium shift collagen synthesis in cloned chondrocytes from type II to type I.[5] Phagocytic leukocytes from rheumatoid synovial fluid contain more type II collagen than type I, which suggests that selective degradation is occurring.[6] Understanding mechanisms such as these, which affect expression of disease, may allow future identification of patients at increased risk for the development of fibrotic sequelae from commonly used drugs such as alcohol and propranolol.

ROBERT C. SIEGEL, MD
San Mateo, California
Associate Clinical Professor of Medicine and Orthopedics University of California, San Francisco School of Medicine

REFERENCES

1. Graham JR: Localized systemic scleroses, *In* Kelly WN, Harris ED, Ruddy S, et al (Eds): Textbook of Rheumatology. Philadelphia, WB Saunders Co, 1981, pp 1235-1254

2. Potter SR, Goldstein S, Bienenstock J: Serum from progressive systemic sclerosis patients activates fibroblast proliferation. Clin Res 29:160A, 1981

3. Botstein GR, Sherer GK, LeRoy EC: Fibroblast selection in scleroderma: A model of fibrosis. Clin Res 29:163A, 1981

4. Vater CA, Harris ED Jr, Siegel RC: Native cross-links in collagen induced resistance to human skin synovial collagenase. Biochem J 181:639-645, 1979

5. Deshmukh K, Kline WG, Sawyer BD: Role of calcium in the phenotypic expression of rabbit articular chondrocytes in culture. FEBS Lett 67:48-51, 1976

6. Gay S, Gay RE, Miller EJ: The collagens of the joint. Arthritis Rheum 23:937-941, 1980

The Changing Cigarette

THE TOBACCO INDUSTRY spent more than $420,000,000 in 1978 to promote lower tar and nicotine cigarettes. This represented 48 percent of all dollars spent for cigarette advertising. Over the past decade lower tar and nicotine cigarettes have claimed a progressively larger share of the United States market, increasing from 4 percent in 1970 to 50 percent in 1979. Part of the switch to lower tar cigarettes appears to be due to acceptance of the implicit advertising message that substantial reductions in machine-measured tar and nicotine levels may be equated with substantial reductions in risk for smokers. Is the changing cigarette really safer than its predecessors? The recently released 1981 Report of the Surgeon General summarizes available data and makes recommendations concerning this question.[1]

The report emphasizes that there is "no safe cigarette and no safe level of consumption." For most tobacco-related diseases the evidence concerning lower tar and nicotine cigarettes is simply too limited to allow judgments about risk reduction. Only in the case of lung cancer were there firm data documenting a modest reduction in disease mortality for smokers of lower tar and nicotine cigarettes compared with smokers of higher tar and nicotine cigarettes; however, these modestly reduced rates were much higher than those of nonsmokers.

The report assists physicians in advising their patients about lower tar and nicotine cigarettes. It cautions about assumptions concerning the safety of lower tar and nicotine cigarettes:

- Compensatory smoking behavior—for example, smoking a greater number of cigarettes or inhaling more frequently—may result in greater smoke exposure and risk for the smoker.
- The increasing use of tobacco additives to enhance consumer acceptability of lower tar and nicotine cigarettes represents an essentially unmeasured risk for the smoker. Some additives are either known carcinogens or give rise to carcinogenic substances during combustion. Because these additives are not regulated by the federal government, public disclosure of substances currently in use is not required.
- Reductions in tar and nicotine yields may not correspond to comparable reductions in other smoke constituents—that is, gas phase constituents may be present in increased concentrations.
- Published machine-smoked tar and nicotine yields do not correspond to individual smoke exposure, and in some cases the exposure may be greatly underestimated.

A burning cigarette is very much like a miniature chemical factory that produces a myriad of toxic substances. Compared with stopping smoking or never starting to smoke, modifying the smoke effluent offers only slight risk reduction for a smoker.

JOHN H. HOLBROOK, MD
Associate Professor, Internal Medicine University of Utah Medical Center Special Editor for Utah Salt Lake City

REFERENCE

1. The Changing Cigarette: A Report of the Surgeon General. US Department of Health and Human Services, Office of the Assistant Secretary for Health, Office on Smoking and Health, 1981, pp 237

CASE REPORTS

Refer to: Herbert DA, Fessel WJ: Idiopathic hypertrophic osteoarthropathy (pachydermoperiostosis). West J Med 134: 354-357, Apr 1981

Idiopathic Hypertrophic Osteoarthropathy (Pachydermoperiostosis)

DAVID A. HERBERT, MD
Los Angeles

W. JEFFREY FESSEL, MD
San Francisco

IDIOPATHIC HYPERTROPHIC OSTEOARTHROPATHY is a syndrome characterized by periosteal new bone formation, clubbing, swelling of joints and skin changes; patients may have one or more of these manifestations.[1,2] The condition is also known as pachydermoperiostosis, acropachyderma with pachyperiostitis, and the Touraine-Solente-Golé syndrome. We recently saw a patient with the characteristic findings of this rare disease; the case illustrates the usually benign course.

Report of a Case

A 72-year-old Filipino man was evaluated for clubbing of the fingers and toes. According to the patient's elder sister, he had had large, unusually shaped extremities since birth. These became progressively thickened through adolescence, but he had noted no further thickening until he was given an unknown lotion 25 years ago for his thick, somewhat pruritic skin. When he applied the lotion to his lower legs, the skin thickened further and became deeply hyperpigmented. Although he had worked as a laborer, he had only occasional arthralgias after strenuous work. He had not noted excessive sweating. To the best of his knowledge, none of his family had been similarly affected.

At physical examination, the patient had normal facial features without thickening of the skin of the forehead. His clavicles were obviously thickened, especially at their medial ends. He had severe clubbing of all fingers and toes (Figure 1). The skin on his lower legs was notably thickened, scaly and blackened. The circumferences of his distal tibiae were visibly increased (Figure 1). He had no bone tenderness; all joints had a full range of motion and were without effusions.

Figure 1.—Clubbing of toes in a 72-year-old man with idiopathic hypertrophic osteoarthropathy (pachydermoperiostosis).

Radiographic examination showed an extreme degree of periostitis in many bones, particularly the distal ends of the tibiae and fibulae (Figure 2), the proximal femora (Figure 3), and the distal radii (Figure 4). There was acro-osteolysis of the distal phalanges of the fingers (Figure 4) and toes (Figure 5). The radiographs showed that the periosteal new bone formation affected the midportion of the diaphyses as well as the epiphyses.

Discussion

Most patients with idiopathic hypertrophic osteoarthropathy develop normally until adolescence, when skin thickening and bone and joint deformities begin to occur. These changes progress for a number of years, then usually stabilize.[1-5] However, some patients, as did ours, may experience these changes at a much earlier age.[6]

The bony changes consist of symmetric, irregu-

From the Department of Medicine, Kaiser-Permanente Medical Center, Los Angeles, and the Department of Medicine, Kaiser-Permanente Medical Center, San Francisco.

This research was supported by the Community Service Program of Kaiser Foundation Hospitals.

Submitted June 6, 1980.

Reprint requests to: W. Jeffrey Fessel, MD, Department of Medicine, Kaiser-Permanente Medical Center, 2200 O'Farrell St., San Francisco, CA 94115.

lar periosteal hypertrophy with new bone formation[3,4]; acro-osteolysis has also been reported.[7] These changes are most severe in the extremities[7] and can involve any bone, although the skull and vertebral column are rarely affected.[1,8] The articular surfaces are spared,[2,9] but intermittent swelling of joints and effusions are common; these are often moderately painful but may be asymptomatic.[1,10]

A considerable degree of painless clubbing usually results from proliferation of the soft tissues of the distal phalanges. This manifestation gives the digits a bulbous appearance, with the nails curving over the hypertrophied nail beds.[1]

Changes of the skin include generalized thickening (pachyderma), hyperhidrosis and seborrheic overactivity.[4] Eczema is also common.[11] The skin thickening and redundancy may become so excessive on the scalp and forehead as to cause a characteristic furrowing, termed cutis verticis gyrata.[1,2] The combination of thickened skin and bony enlargement can result in great thickening of the extremities, which is often the most striking physical finding.

On histological examination, involved bones

Figure 2.—Radiograph showing periostitis in distal ends of tibiae and fibulae.

Figure 3.—Radiograph showing extreme periostitis in proximal femur (arrow).

Figure 4.—Radiograph showing acro-osteolysis of fingers affecting the middiaphysis and epiphyses.

Figure 5.—Radiograph showing acro-osteolysis of toes.

show periosteal proliferation with round cell infiltration and new bone formation between the periosteum and the original cortex. This new bone later fuses with the old.[4] Hypertrophy of the nutrient arteries occurs.[1,4] Gradually the skin shows thickening and hyalinization of collagen and elastic fibers with interposed foci of necrosis and inflammation. The sebaceous and sweat glands become hypertrophied, as do the hair follicles.[4]

Most patients have only moderate discomfort from this disease and are able to lead normal lives, as did our patient. Although their main complaints often relate to their appearance and to hyperhidrosis,[2,4] more serious problems occasionally develop. Skin thickening of the eyelids may be severe enough to cause ptosis, which requires surgical correction.[1,8] Thickening of the skull has been considered responsible for a facial nerve palsy.[1] Finally, there are rare reports of bone marrow failure and extramedullary hematopoiesis attributed to destruction of the marrow by idiopathic hypertrophic osteoarthropathy.[12,13]

In 40 percent to 50 percent[2,4] of reported cases there is a familial history of idiopathic hypertrophic osteoarthropathy; family members, predominantly male, often had incomplete forms of the disease. Analysis of findings on studies of kindreds suggests that the condition may be inherited as an autosomal dominant trait with variable penetrance, which is most severe in males.[2]

Our patient's condition reflected many of these aspects of idiopathic hypertrophic osteoarthropathy. He had a great degree of periosteal new bone formation and clubbing, with notable thickening of the skin of his lower legs, although there was no hyperhidrosis or cutis vertieis gyrata. The absence of progression of the disease in adulthood is typical.

Idiopathic hypertrophic osteoarthropathy should be compared with secondary hypertrophic osteoarthropathy, also known as pulmonary osteoarthropathy. The latter occurs as a complication of many diseases, especially thoracic infections and malignant conditions, but also of cardiac and gastrointestinal disorders and extrathoracic neoplasms as well.[10,11] The presenting features of pulmonary osteoarthropathy are similar to those of idiopathic hypertrophic osteoarthropathy, although the anatomic changes are usually less pronounced and the resulting discomfort more severe than in the idiopathic syndrome.[4] The two are usually differentiated by a history of early onset of the idiopathic hypertrophic osteoarthropathy, whereas pulmonary osteoarthropathy usually develops in association with a primary process. The osteoarthropathy, however, may precede clinical evidence of the underlying disease by several months.[11] A history of similarly affected family members may suggest idiopathic hypertrophic osteoarthropathy.

In contrast to the secondary form of the disease, which often improves with therapy of the underlying process,[11] there is no available therapy for the idiopathic hypertrophic osteoarthropathy. Fortunately, most patients with the latter condition have no more than moderate disability from their disease and have normal life spans.[1,5]

Summary

Idiopathic hypertrophic osteoarthropathy usually is a benign syndrome characterized by periosteal new bone formation, clubbing, swelling of joints and thickened, furrowed skin. Evaluation of a patient with this rare condition showed the clubbing and skin thickening, as well as radiographic changes in the distal ends of the tibiae and fibulae, proximal femora and distal radii, with acro-osteolysis of the distal phalanges of the fingers and toes. Clinicians can differentiate between idiopathic hypertrophic osteoarthropathy and secondary osteoarthropathy mainly by a history of early onset of the former, often with a positive family history, and the coexistence of pulmonary, gastrointestinal or neoplastic disease in the latter.

REFERENCES

1. Camp JD, Scanlan RL: Chronic idiopathic hypertrophic osteoarthropathy. Radiology 50:581-594, 1948

2. Rimoin DL: Pachydermoperiostosis (idiopathic clubbing and periostosis): Genetic and physiologic considerations. N Engl J Med 272:923-931, 1965

3. Greenfield GB: Radiology of Bone Diseases, 2nd Ed. Philadelphia, JB Lippincott Co, 1975, pp 385, 389

4. Vogl A, Goldfischer S: Pachydermoperiostosis: Primary or idiopathic hypertrophic osteoarthropathy. Am J Med 33:166-187, 1962

5. Brugsch HG: Acropachyderma with pachyperiostitis. Arch Intern Med 68:687-700, 1941

6. Bartolozzi G, Bernini G, Maggini M: Hypertrophic osteoarthropathy without pachyderma: Idiopathic form. Am J Dis Child 129:849-851, 1975

7. Guyer PB, Brunton FJ, Wren MW: Pachydermoperiostosis with acro-osteolysis: A report of five cases. J Bone Joint Surg [Br] 60B:219-223, 1978

8. Bhate DV, Pizarro AJ, Greenfield GB: Idiopathic hypertrophic osteoarthropathy without pachyderma. Radiology 129: 379-381, 1978

9. Shawarby K, Ibrahim MS: Pachydermoperiostosis: A review of the literature and report of four cases. Br Med J 1:763-766, 1962

10. Susmano A, Shah P, Tashima CK: Idiopathic hypertrophic osteoarthropathy. Am Heart J 76:582-584, 1968

11. Currarino G, Tierney RC, Giesel RG, et al: Familial idiopathic osteoarthropathy. Am J Roentgenol Radium Ther Nucl Med 85:633-644, 1961

12. Neiman HL, Gompels BM, Martel W: Pachydermoperiostosis with bone marrow failure and gross extramedullary hematopoiesis. Radiology 110:553-554, 1974

13. Metz EN, Dowell A: Bone marrow failure in hypertrophic osteoarthropathy. Arch Intern Med 116:759-764, 1965

Refer to: Byrd WE, Hunt RE, Burgess R: Retroperitoneal fibrosis as a cause of fever of undetermined origin. West J Med 134:357-361, Apr 1981

Retroperitoneal Fibrosis as a Cause of Fever of Undetermined Origin

CDR WILLIAM E. BYRD, MC, USN
LCDR ROBERT E. HUNT, MC, USN
LCDR RICHARD BURGESS, MC, USN
Portsmouth, Virginia

A CONSULTING RHEUMATOLOGIST is sometimes asked to offer his expertise in seeking the cause of a multisystem illness that includes fever, arthralgias, myalgias, anorexia, weight loss, anemia and elevated sedimentation rate. Invariably, consultants in hematology, oncology, endocrinology, gastroenterology and infectious diseases have eliminated illnesses that would fall primarily within their domain. Almost as an afterthought, a rheumatologist is called in to "rule out vasculitis" or "exclude an evolving connective tissue disease." The present case report and discussion emphasize another entity whose prodrome can mimic a multitude of systemic illnesses. Though well described in the surgical literature, it merits more critical attention by internists and rheumatologists in their efforts to offer a more comprehensive differential diagnosis in the workup of a chronically ill patient.

From the Divisions of Rheumatology and Pathology, Naval Regional Medical Center, Portsmouth, Virginia.

Submitted, revised, December 22, 1980.

Reprint requests to: LCDR Richard Burgess, MC, USN, Division of Pathology, Naval Regional Medical Center, Portsmouth, Virginia 23708.

Report of a Case

A 21-year-old Marine was in excellent health until late October 1979 when a sensation of fullness in the right ear developed, followed by a temperature rising to 38.9°C (102°F), nonshaking chills, anorexia and fatigue. Studies were done at the medical clinic and a diagnosis of right-sided otitis media was made. Ampicillin and erythromycin were prescribed sequentially without improvement. His fever persisted accompanied by arthralgias of the elbows, wrists, knees and ankles as well as a retrobulbar headache without photophobia. Because the symptoms persisted, the patient was admitted to hospital at the Naval Regional Medical Center, Camp Lejeune, North Carolina, on November 5, 1979. On admission, a physical examination documented a temperature of 38°C (100.4°F). There were multiple, small, nontender posterior, cervical and supraclavicular nodes. Liver span was 12 cm and the spleen was soft, nontender and palpable 2 cm below the left costal margin. Humeroulnar joints and wrists were tender to palpation without obvious synovial thickening. Initial laboratory test results included a hematocrit of 30 percent, with a leukocyte count of 10,200 per cu mm and a normal differential. Platelet count was 178,000 per cu mm. Westergren sedimentation rate was 130 mm per hour. A peripheral blood smear was hypochromic. The following studies gave normal or negative findings: SMA-18, hepatitis-associated antigen, mononucleosis spot test, cold agglutinins, VDRL, Coombs direct and indirect tests, latex fixation, fluorescent antinuclear antibody (FANA) and analysis of the urine. Multiple blood cultures were negative. Purified protein derivative-standard (PPDS) and streptokinase-streptodornase (SKSD) skin tests were nonreactive. Additional studies included a bone marrow aspirate, which showed myeloid and megakaryocytic hyperplasia. A left posterior cervical node biopsy showed lymphoid hyperplasia. Adult Still disease was considered a reasonable possibility at this time, and high-dose salicylate therapy was initiated. The fever abated somewhat but the hematocrit decreased to 23 percent, with a hypo-

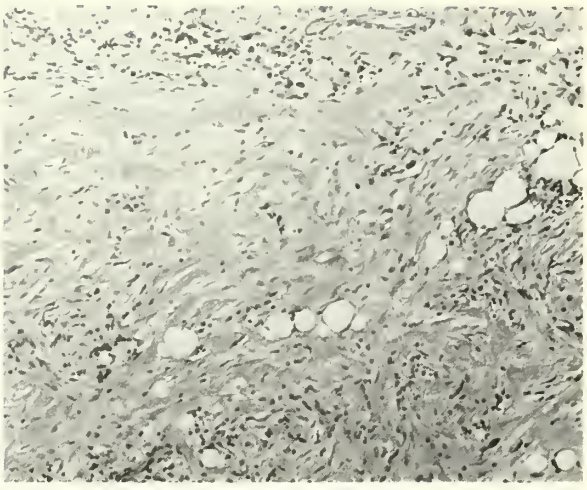


Figure 1.—A retroperitoneal biopsy specimen showing diffuse fibrosis with entrapment of adipose tissue and a lymphoplasmacytic infiltrate with eosinophils (reduced from approximately 100×).

chromic, microcytic blood smear. There was no evidence of loss of blood. Because the symptoms persisted, the patient was transferred to the Naval Regional Medical Center, Portsmouth, Virginia, where he remained in hospital from 11 December 1979 to 21 February 1980. Vital signs on admission were normal with the exception of a temperature of 38.6°C (101.4°F). A spleen tip was palpable. During his stay in hospital, a hectic fever persisted in association with drenching night sweats. An exhaustive workup was initiated. Serological studies gave normal or negative findings for antinuclear antibody (ANA), latex fixation, thyroid panel, serum B_{12}, serum folate, C-3, C-4, CH-50, toxoplasmosis and cytomegalovirus titers, and α-fetoprotein; a urine test for human chorionic gonadotropin was negative. The alkaline phosphatase level was 254 units (normal 40 to 115). An SKSD skin test was reactive. An x-ray study of the chest, sinus series and intravenous pyelogram (IVP) showed no abnormalities. A liver-spleen scan and gallium scan demonstrated hepatosplenomegaly without focal defects. A bone scan as well as upper gastrointestinal and small bowel studies showed no abnormalities. An abdominal computed tomographic (CT) scan gave negative results. Procedural studies, including endoscopy, proctosigmoidoscopy, lumbar puncture and percutaneous liver biopsy, gave negative results as well. A bone marrow aspirate again showed hyperplasia of all the cell lines. During his time in hospital, the patient remained anorectic and febrile and lost 20 pounds. In view of his clinical deterioration, with spiking fevers and anemia that required transfusion, an exploratory laparotomy was done on January 24, 1980. The preoperative diagnosis was abdominal lymphoma.

At laparotomy, a large mass (6×8×4 cm) was found in the rectosigmoid area at the brim of the sacrum, inferior to the rectum, appearing adherent to the bowel but easily separated. Frozen sections indicated fibrosis and inflammation. Permanent sections showed changes consistent with retroperitoneal fibrosis, with areas of dense refractile collagen laid down in a haphazard arrangement (see Figure 1). The fibrosis was accompanied by an inflammatory infiltrate composed of lymphocytes, plasma cells and eosinophils. Some sections showed destruction and entrapment of adipose tissue. A prominent feature of the biopsy specimens was a chronic vasculitis which appeared to be primarily centered around venules (Figure 2). Immunofluorescent studies were not done on the unfixed specimen. Subsequently, immunoperoxidase studies were obtained on the formalin-fixed tissue and were negative. Biopsies of the liver, spleen and mesenteric nodes gave negative results. A diverting colostomy was carried out. Postoperatively, the patient continued to have spiking temperatures from 39° to 40°C (102.2° to 104°F). On February 12, after all special stains as well as fungal and acid-fast bacilli cultures were reported as negative, prednisone therapy was initiated in a dosage of 15 mg four times a day. Fever resolved within 48 hours. Corticosteroid therapy was gradually tapered over 3½ months and discontinued at the end of May. The hematocrit at that time was 44 percent, with a normal sedimentation rate. During this time, the patient regained 20 pounds. The colostomy was revised on June 30 and the patient has continued to remain asymptomatic and afebrile.

Discussion

Since Ormond established idiopathic retroperitoneal fibrosis as a clinical entity in 1948,[1] more than 600 cases have been reported in the medical and surgical literature. Most cases, however, have emphasized obstructive phenomena as well as diagnostic and therapeutic approaches, with less attention given to systemic manifestations. That the latter feature may be unfamiliar to many general internists and medical subspecialists, is suggested by the fact that the four largest reviews of retroperitoneal fibrosis have appeared in the

surgical and radiological literature,[2-5] with constitutional symptoms given only passing reference in recent editions of two major medical texts.[6,7] The entity is not even mentioned in the most recent edition of a standard rheumatology text.[8]

The critical importance of retroperitoneal fibrosis to internists in general, and to rheumatologists in particular, is amply illustrated by both its propensity to occur in the fifth and sixth decades and its varied presenting signs, symptoms and serological test findings. The most prominent of these are: back pain,[1] abdominal pain,[9] intermittent claudication,[10] headache,[11] Raynaud phenomenon,[12] hypertension,[13] pericardial friction rub,[14,15] pleural effusion,[15] splenomegaly,[3] fever, weight loss, anorexia, increased sedimentation rate and hyperglobulinemia.[16] Certainly, a reasonable differential diagnosis of the above might include the following: granulomatous diseases such as tuberculosis or sarcoidosis,[17] adult Still disease,[18] systemic lupus erythematosus,[19] periarteritis nodosa,[20] giant cell arteritis,[21] Whipple disease,[22] T-3 toxicosis,[23] atrial myxoma,[24] bacterial endocarditis[25,26] and neoplasm.[27] Many of these illnesses, of course, respond partially or completely to corticosteroid therapy. One cannot help but wonder whether some cases of biopsy-negative giant cell arteritis, ANA-negative lupus, and presumptive adult Still disease (without the characteristic rash) have represented undiagnosed retroperitoneal fibrosis.

Many publications have suggested more than a coincidental association between retroperitoneal fibrosis and connective tissue diseases.[28-31] Since the relationship between methysergide maleate (Sansert) and retroperitoneal fibrosis was extensively reviewed in 1966,[32] many have postulated that the condition represents a hypersensitivity response to a variety of antigens including bacterial, fungal, tuberculous, tumor-associated and drug-hapten combinations.[2,3,16] Support for this premise can be found in a number of case reports documenting a small-vessel vasculitis with all lesions in a similar stage of evolution.[12,15,33,34] Additionally, several recent reports have documented the presence of immunofluorescence[35] as well as immune complex glomerulonephritis with IgG and C-3 deposition.[36] In several instances, connective tissue illnesses have antedated retroperitoneal fibrosis by many years or have been associated with Dupuytren contracture,[37] Peyronie disease,[15,38] idiopathic mediastinal fibrosis,[39,40] Riedel thyroiditis,[39,41] and pulmonary fibrosis,[12,39] further supporting a localized response in a susceptible host to chronic antigenic challenge. Histopathological studies obtained earlier in the illness have consistently demonstrated an intense infiltration of mononuclear cells, predominantly lymphocytes, plasma cells and eosinophils.[11] Biopsy specimens obtained later in the disease process have demonstrated a predominantly fibrotic change.[5] The encouraging responses to corticosteroids in the early cellular phase are all compatible with a primary immune mechanism.

The present case report is most intriguing because it illustrates another cause of fever of undetermined origin in adults. Although another publication indirectly alludes to this type of presentation,[34] retroperitoneal fibrosis as the cause of a prolonged fever was not mentioned in several

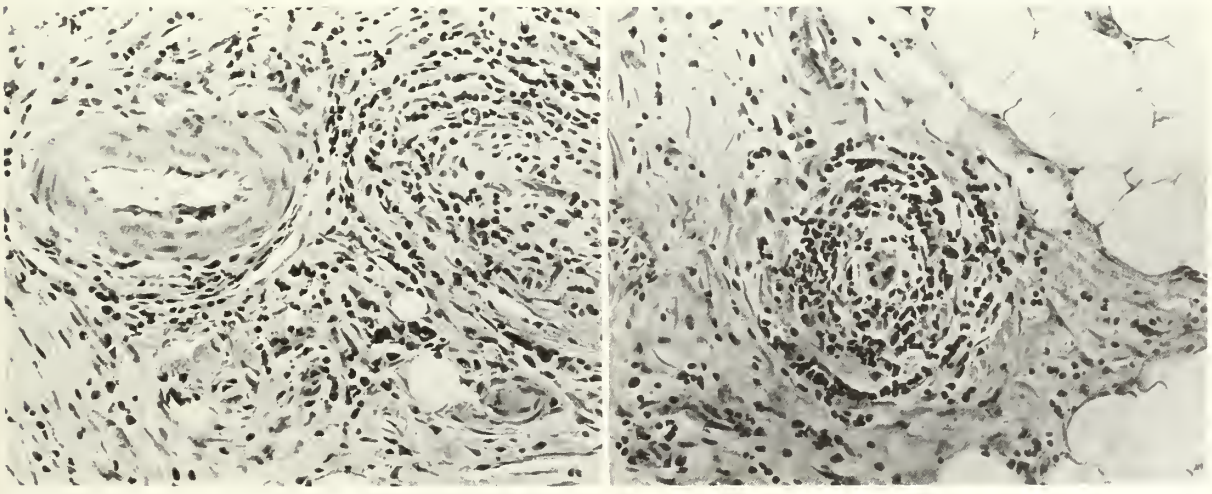


Figure 2.—Left, Area of vasculitis showing minimal involvement of a small arteriole and obliterative venulitis. **Right,** Obliterative venulitis with many plasma cells and lymphocytes (reduced from approximately 400×).

large reviews of fever of undetermined origin in adults and children.[42-44] While our patient's workup was careful and systematic, the diagnosis was not suspected before laparotomy. In this instance, the IVP failed to show the classic triad of medial deviation of the ureters, bilateral ureteral narrowing, and dilatation of calices and pelvis.[45] Sophisticated noninvasive tests were not helpful.[38,46] In retrospect, had a barium enema study been done and had the CT scan included the pelvis, the rectosigmoid mass undoubtedly would have been discovered before laparotomy. Fortunately, the patient's response to corticosteroid therapy was excellent.

As in many connective tissue illnesses (such as Wegener granulomatosis, giant cell arteritis and polyarteritis nodosa), early diagnosis is critically important to prevent death or permanent damage to organs. It is hoped that greater awareness of retroperitoneal fibrosis as a cause of fever of undetermined origin may facilitate early diagnosis and a favorable response to corticosteroid therapy. Unfortunately, current guidelines for dosage and duration of such steroid therapy are imprecise and the long-term prognosis is unknown.[47,48] Further investigations are needed to solve these problems.

Summary

Idiopathic retroperitoneal fibrosis (Ormond disease) has been recognized as a cause of obstructive uropathy for more than 70 years. Less well known is its association with profound constitutional disease, as well as with many connective tissue illnesses. Recent observations of dramatic clinical responses to corticosteroid therapy as well as pathological studies confirming intense perivascular inflammation and positive immunofluorescence argue persuasively for immune complex-mediated injury. This case report establishes one more cause for fever of undetermined origin and reviews the clinical features of an entity that should be familiar to every internist and rheumatologist.

REFERENCES

1. Ormond JK: Bilateral ureteral obstruction due to envelopment and compression of an inflammatory retroperitoneal process. J Urol 59:1072-1079, 1948

2. Koep L, Quidema G: The clinical significance of retroperitoneal fibrosis. Surgery 81:250-257, 1977

3. Lepor H, Walsh P: Idiopathic retroperitoneal fibrosis. J Urol 122:1-6, 1979

4. Arger P, Stolz J, Miller W: Retroperitoneal fibrosis: An analysis of clinical spectrum and roentgenographic signs. Am J Roentgenol Radium Ther Nucl Med 119:812-821, 1973

5. Hache L, Utz D, Woolner L: Idiopathic fibrous retroperitonitis. Surg Gynecol Obstet 115:737-744, 1962

6. Beeson PB, McDermott W (Eds): Textbook of Medicine, 15th Ed. Philadelphia, WB Saunders Co, 1979, pp 223-224

7. Thorn GW (Ed): Harrison's Principles of Internal Medicine, 9th Ed. Philadelphia, McGraw-Hill Book Co, 1980, pp 25, 1353

8. McCarty DJ (Ed): Arthritis and Allied Conditions, 9th Ed. Boston, Lea and Febiger, 1979

9. Jones JH, Ross EJ, Matz LR, et al: Retroperitoneal fibrosis. Am J Med 48:203-208, 1970

10. Watts HG: Retroperitoneal fibrosis. NZ Med J 78:247-251, 1973

11. Mitchinson MJ: The pathology of idiopathic retroperitoneal fibrosis. J Clin Pathol 23.681-690, 1970

12. Que GS, Mandema E: A case of idiopathic retroperitoneal fibrosis presenting as a systemic collagen disease. Am J Med 36:320-329, 1964

13. Case 13-1976, Case records of the Massachusetts General Hospital: Weekly clinicopathologic exercises. N Engl J Med 294: 712-720, Mar 25, 1976

14. Kay RG: Retroperitoneal fibrosis with perivascular fibrosis. Br J Urol 35:284-292, 1963

15: Reidbord H, Hawk W: Idiopathic retroperitoneal fibrosis and necrotizing vasculitis. Cleveland Clin Quart 32:19-27, 1965

16. Zabetakis P, Novich R, Matarese R, et al: Idiopathic retroperitoneal fibrosis: A systemic connective tissue disease. J Urol 122:100-102, 1979

17. Case 42-1976, Case records of the Massachusetts General Hospital: Weekly clinicopathological exercises. N Engl J Med 295:885-892, Oct 14, 1976

18. Bujak J, Aptekar R, Decker J, et al: Juvenile rheumatoid arthritis presenting in the adult as fever of unknown origin. Medicine 52:431-444, 1973

19. Case 42-1979, Case records of the Massachusetts General Hospital: Weekly clinicopathologic exercises. N Engl J Med 301: 881-887, Oct 18, 1979

20. Case 5-1979, Case records of the Massachusetts General Hospital: Weekly clinicopathologic exercises. N Engl J Med 300: 243-252, Feb 1, 1979

21. Ghos EM, Shensa S, Lerner P: Arteritis of the aged (giant cell arteritis) and fever of unexplained origin. Am J Med 60: 429-436, 1976

22. Pastor B, Geerken R: Whipple's disease presenting as pleuropericarditis. Am J Med 55:827-831, 1973

23. Simon H, Daniels G: Hormonal hyperthermia: Endocrinologic causes of fever. Am J Med 66:257-262, 1979

24. Byrd W, Matthews O, Hunt R: Left atrial myxoma presenting as a systemic vasculitis. Arthritis Rheum 23:240-243, 1980

25. Churchill M, Geraci J, Hunder G: Musculoskeletal manifestations of bacterial endocarditis. Ann Intern Med 87:754-759, 1977

26. Heffner JE: Extracardiac manifestations of bacterial endocarditis. West J Med 131:85-91, Aug 1979

27. Caldwell DS: Musculoskeletal syndromes associated with malignancy. Semin Arthritis Rheum 10:198-223, Feb 1981

28. Schnitzler JK, Verret C, Caron E, et al: Fibrosclerose multifocale (mediastinale, retroperitoneale, pelvienne, avec mesenterite retractile) associee a une vascularite et revelee par un livedo (English abstract). Ann Dermatol Venereol (Paris) 105:943-956, 1978

29. Lipman R, Johnson B, Berg G, et al: Idiopathic retroperitoneal fibrosis and probable systemic lupus erythematosus. JAMA 96:204-206, 1966

30. Blau E: Relapsing polychondritis and retroperitoneal fibrosis in an 8-year-old boy. Am J Dis Child 130:1149-1152, 1976

31. Lloyd D, Balfe J, Barkin M, et al: Systemic lupus erythematosus with signs of retroperitoneal fibrosis. J Pediatr 85:226-228, 1974

32. Gram J, Suby H, LeGompte P, et al: Fibrotic disorders associated with methysergide therapy for headache. N Engl J Med 274:359-368, 1966

33. Hellstrom H, Perez-Stable EC: Retroperitoneal fibrosis with disseminated vasculitis and intrahepatic sclerosing cholangitis. Am J Med 40:184-187, 1976

34. Jones EA, Alexander MK: Idiopathic retroperitoneal fibrosis associated with an arteritis. Ann Rheum Dis 25:356-359, 1966

35. Leoni S, Rondanelli E: Immunofluorescence in the study of sclerosing retroperitonitis. Urol Int 34:55-61, 1979

36. Katz S, Batts O, Yodis M, et al: Immune complex glomerulonephritis in a case of retroperitoneal fibrosis. Am J Clin Pathol 67:436-439, 1977

37. Hoffman WW, Trippe OH: Retroperitoneal fibrosis: Etiologic considerations. J Urol 86:222-231, 1961

38. Sterzer S, Herr H, Mintz I: Idiopathic retroperitoneal fibrosis misinterpretated as lymphoma by computed tomography. J Urol 122:405-406, 1979

39. Comings DE, Skubi KB, VanEyes J, et al: Familial multifocal fibrosclerosis: Findings suggesting that retroperitoneal fibrosis, mediastinal fibrosis, sclerosing cholangitis, Riedel's thyroid, and pseudotumor of the orbit may be different manifestations of a single disease. Ann Intern Med 66:884-892, 1967

40. Cameron DG, Ing ST, Boyle M, et al: Idiopathic mediastinal and retroperitoneal fibrosis. Can Med Assoc J 85:227-232, 1961

41. Bartholomew LG, Cain JC, Woolner LB, et al: Sclerosing cholangitis: Its possible association with Riedel's struma and fibrous retroperitonitis: Report of two cases. N Engl J Med 269: 8-12, 1963

42. Petersdorf R, Beeson P: Fever of unexplained origin: Report of 100 cases. Medicine 40:1-30, 1961

43. Esposito A, Klekman R: A diagnostic approach to the adult with fever of unknown origin. Arch Intern Med 139:575-579, 1979

44. Pizzo P, Lovejoy F, Smith D: Prolonged fever in children: Review of 100 cases. Pediatrics 55:468-473, 1975

45. Persky L, Huus J: Atypical manifestations of retroperitoneal fibrosis. J Urol 111:340-344, 1974

46. Jacobson J, Redmond H: Ultrasound findings in a case of retroperitoneal fibrosis. Radiology 113:423-424, 1974

47. Morandi LP, Grub PJ: Retroperitoneal fibrosis: Response to corticosterod therapy. Arch Intern Med 128:295-298, 1971

48. Moody T, Vaughn ED: Steroids in the treatment of retroperitoneal fibrosis. J Urol 121:109-111, 1979

Refer to: Shaffer JO: Treatment of agenesis of the diaphragm and esophageal crura—An 18-year follow-up. West J Med 134:361-363, Apr 1981

Treatment of Agenesis of the Diaphragm and Esophageal Crura

An 18-Year Follow-up

J. ORDIE SHAFFER, MD
Hayward, California

When complete prosthetic replacement of a missing vital body part with an implant is done for the first time, serious questions arise: Will the prosthesis expand as the implant grows? If not, will bodily deformity result from the restrictions, thereby making eventual replacement of the prosthesis necessary?

In considering a prosthetic implant to replace a missing left diaphragm and esophageal crura, it was felt that a porous mesh prosthesis rather than a solid one would adapt best to an infant's growth.[1] This hypothesis was supported by experiments in animals[2] in which growth of surrounding tissues into mesh implants suggested that such a prosthetic implant would continue to change in size and contour in accordance with the animal's growth. Studies by Debakey and co-workers[3,4] had shown that a porous Dacron graft used to replace the aorta of a patient had enlarged with the patient's own growth. It appeared that secondary replacement would not be necessary. This approach, it was hoped, could be applied to the replacement of other bodily parts. An 18-year follow-up report of such a case, examining these points, is presented.

Dr. Shaffer is in private practice in Hayward, California.

Submitted, revised, April 23, 1980. Adapted from a paper presented to the Chinese Medical Association at Wuhan, China, on October 13, 1979.

Reprint requests to: J. Ordie Shaffer, MD, 1375 B Street, Hayward, CA 94541.

Report of a Case

A newborn infant presented 18 years ago in a moribund cyanotic state with a scaphoid abdomen and poor chest expansion on both sides but more limited on the left. Breath sounds were absent on the left side of the chest and no masses were palpable in the abdomen. X-ray studies showed abdominal viscera in the left side of the chest, with a compression of the right lung that was consistent with a large congenital diaphragmatic hernia. An emergency laparotomy was done 12 hours after birth, and instead of a partial diaphragmatic defect, a complete absence of the left diaphragm and esophageal crura was found. Also, the stomach and large portions of the small bowel and colon were protruding into the chest, pushing the mediastinum to the right (Figure 1). With not even a remnant of diaphragm, it was apparent that some type of implant was necessary. With the use of a solid prosthesis or impermeable fine mesh, it was probable that, even with a successful implant, the prosthesis might have to be changed later as the infant grew. It was hoped that a porous mesh Dacron graft would enlarge with the child's growth, making this replacement unnecessary.

A preclotted graft was sewn to the periosteum of the ribs and the synthetic esophageal crura, sutured to the small neonatal esophagus, fashioned to keep the stomach in the abdominal cavity. An effective air-tight seal soon formed a new diaphragm, and within two weeks the rudimentary lung expanded and the infant was discharged in a satisfactory condition on the 19th postoperative day.

The mesh diaphragm and esophageal crura became a vital part of the child's own tissues and expanded with the child's normal growth pattern. Periodic x-ray studies of the chest showed that the synthetic graft was continuing to expand as the child grew; thus, deformity was prevented. At 18 months of age, x-ray studies (after oral administration of barium) showed that the synthetic mesh esophageal crura, which had now become an inherent part of the child's tissues, were continuing to function to prevent esophageal reflux (Figure

2). This expansion with maintenance of function has continued to adulthood—the patient is now 18 years of age (Figure 3).

When the child was 6 years old, an operation to excise a scarred atretic testicular remnant adjacent to the left kidney permitted visualization of the new diaphragm and esophageal crura. The left diaphragm was intact and, although the area was now several times the size of the original graft, the margin of the prosthesis was not discernible on the smooth fibrous area forming the new diaphragm. Downward passive movement of the diaphragm was discernible each time the lungs were inflated by the anesthesiologist, indicating that the prosthesis was flexible and not simply a stiff partition. The synthetic esophageal crura had also expanded such that no constriction was present at the esophageal junction; instead, they appeared like normal innate crura and were acting as an efficient mechanism to keep the stomach below the diaphragm and to prevent reflux. The growth of the new diaphragm had continued as in a normal structure.

At 18 years of age the patient is 6 feet tall, has

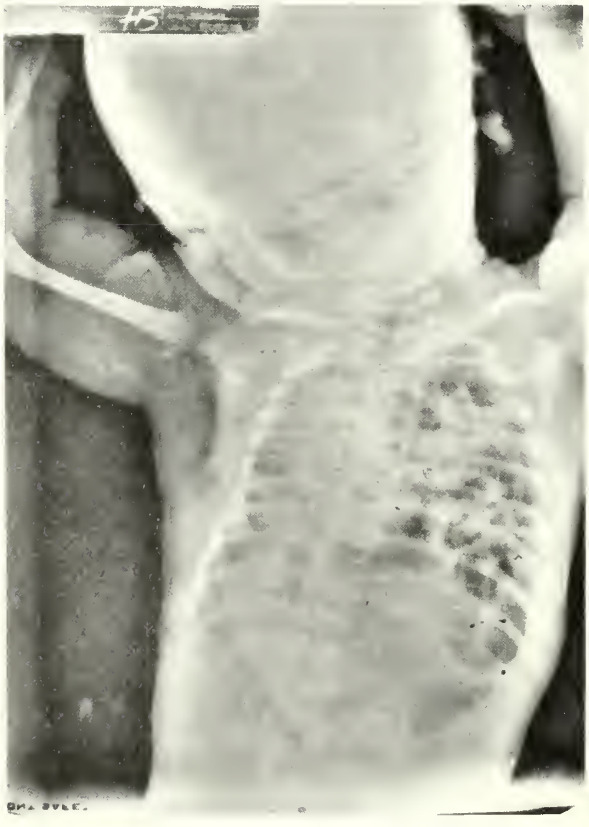


Figure 1.—A roentgenogram of the chest taken 11 hours after birth, showing multiple viscera in the left side of the chest and compression of the right lung.

Figure 2.—A roentgenogram of the chest (following oral administration of barium) taken when the patient was 18 months of age, showing intact prosthetic diaphragm and esophageal crura expanding with the child's growth but continuing to prevent esophageal reflux.

Figure 3.—A roentgenogram of the patient's chest at 18 years of age, showing full adult growth of intact grafted diaphragm and esophageal crura from the small implant placed 12 hours after birth.

an above average exercise tolerance in a three-mile run and plays the trumpet in an orchestra. X-ray studies of the upper gastrointestinal tract, including Trendelenburg positioning, show that the Dacron esophageal crura have enlarged in correlation with the young man's normal growth and still maintain correct abdominal positioning of the stomach to prevent esophageal reflux.

Comment

The small Dacron porous graft used for the esophageal crura and diaphragm continued to enlarge in a normal growth and contour pattern over 18 years, acting as an efficient mechanism to prevent esophageal reflux. Because the graft expanded in normal stages esophageal obstruction did not occur. The gradual enlargement of the synthetic diaphragm prevented deformity of the rib margin, and the diaphragm was able to move passively as in an inherent structure without phrenic innervation.

Summary

Synthetic Dacron mesh used to replace the congenitally absent esophageal crura and diaphragm enlarged as part of a normal growth pattern over 18 years from the patient's birth to adulthood. This suggests that the growth and contour pattern of a small mesh graft in a newborn may be favorably influenced by ingrowth of the surrounding tissues, leading to a large, normally contoured graft in the adult as occurred in this first reported case of successful treatment for agenesis of the diaphragm and esophageal crura.

REFERENCES

1. Shaffer JO: Prosthesis of agenesis of the diaphragm. JAMA 188:1000-1002, Jun 15, 1964
2. Girvin GW: Teflon fabric grafts in growing pigs. Surgery 42:710-716, Oct 1957
3. DeBakey ME, Cooley DA, Crawford ES, et al: Clinical application of a new flexible knitted Dacron arterial substitute. Arch Surg 77:Nov, 1958
4. DeBakey ME, Crawford ES, Cooley DA, et al: Aneurysm of abdominal aorta—Analysis of results of graft replacement therapy one to eleven years after operation. Ann Surg 160:622-639, 1964

Treatment and Prevention of Pelvic Infection

CAN WE START to prevent infectious processes? Yes, we can. We have to think about what we are doing. Can we lower the amount of bacteria? Yes, we can if we use a lavage in some of our patients, if we select our patients appropriately and if we drain correctly. We should not use, for example, a two-way drain (such as a Penrose). If we can use a closed vacuum system, it does lower wound infection. . . . What I use primarily is a cholecystectomy T-tube. It works very nicely. If you are doing an abdominal hysterectomy, you can use a #16 T-tube. It will fit very nicely on a Hemovac. . . . There are other closed-system drains that can be used; these are far superior to the Penrose type of drainage. Can we do other things? Yes, we can. What about shaving our patient just before the operative procedure? Here again, looking at close to 40,000 wounds has shown that shaving the night before doubles the clean-contamination rate. . . . What has been shown very recently is that the last and most important step is that the oxidating metabolic step that is required for bacterial killing is inactivated in the reducing environment of abscess and of deep soft tissue infection. But most important, we need to go back to some of the teachings of Semmelweis and Halsted: we must maintain good surgical techniques, not leave large pedicles, not leave dead space, utilize minimal amount of surgical material, understand what a foreign body (such as an IUD) really is and think about what we are doing to our patients. Then, we can start to understand infection and start to prevent it.

—RUDOLF P. GALASK, MD, *Iowa City*

Extracted from *Audio-Digest Obstetrics and Gynecology*, Vol. 27, No. 17, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1577 East Chevy Chase Drive, Glendale, CA 91206.

Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

Infirmaries: A Way to Reduce Medical Costs?

TO THE EDITOR: I work at a student health service where we have an inpatient facility that can and does provide excellent inpatient service for the vast majority of the illnesses with which our students become afflicted. Our infirmary is not equipped to handle the most dire of emergencies, but for most inpatient illnesses, it functions admirably. The cost per patient day in our infirmary is about $100. This is in spite of the fact that we have an extremely low utilization, hovering between 7 percent and 8 percent of capacity. Certainly, if our utilization were higher, the cost per patient-day would be proportionately less. It seems to me that this kind of facility might very well have a place as an option for the general public. When afflicted with low back pain requiring bed rest, pneumonia, mild psychological decompensations and so on, hospital care in a typical acute care hospital is an exceptionally expensive option. Private infirmaries, either separate from or attached to existing hospitals, could potentially reduce the cost of medical care dramatically.

ED SARGENT, MD
Student Health Center
Oregon State University
Corvallis, Oregon

Therapy for Ankylosing Spondylitis

TO THE EDITOR: I was interested in the author's statement in the February 1981 Medical Staff Conference on seronegative spondyloarthritis[1] that the cornerstone of treatment of ankylosing spondylitis is physical therapy. In this article, he also states that collars and braces are relatively ineffective in the prevention and treatment of deformity. He also states that drug therapy does not appear to retard the progression of spinal ankylosis. It is my impression that it has never been proved that physical therapy is of any benefit in the prevention of spinal deformity. While I would agree that it is of definite benefit in the prevention of hip flexion contracture, the major disabling deformity of ankylosing spondylitis is the thoracic kyphosis.

If the author has any reference to a scientific study of the long-term benefit of physical therapy, I would be interested in reading it. The debate seemed to resemble that which for so long revolved about the question of the benefits of physical therapy in scoliosis. The many years of investigation have shown that physical therapy does not prevent the progression of scoliotic curves and that long-term bracing will only hold but not correct an established curve.

If it has been established that bracing does not prevent thoracic kyphosis in ankylosing spondylitis, it is difficult for me to understand how physical therapy can accomplish this.

RICHARD A. MAUN, MD
Whittier, California

REFERENCE

1. Wofsy D: Seronegative spondylarthritis—Medical Staff Conference, University of California, San Francisco. West J Med 134:134-140, Feb 1981

Diet Not Shown Effective in Psoriasis

TO THE EDITOR: This relates to the letter about psoriasis and diet in the November 1980 issue. The letter, by Dr. Douglass, shows a naive understanding of the literature as it pertains to psoriasis. There is a host of evidence that relates the negative relationship between carbohydrates and psoriasis. The skin-gut school of philosophy was once rampant among dermatologists and seems now to be courted by nondermatologists who do not know the literature. Man's age-old desire to control disease always turns to manipulation of the diet. Cure is always seen around the bend of the breakfast bowl. Numerous studies where patients were put into hospitals and carefully observed showed that specific and special diets helped.[1-5] What the observers failed to realize is that any patient with psoriasis (and with hypertension, and with ulcer disease and with chronic mild renal disease) does well with hospital care and intensive observation.

The data presented of one specific patient sub-

jectively observed for several years are meaningless when you deal with a disease as complex as psoriasis. I hope that the readers of the earlier letter did not advise the elimination of fruits and milk to their patients. I do not want to refer these patients to my fellow internists with preliminary diagnoses of vitamin deficiencies and calcium loss.

MARVIN RAPAPORT, MD
Department of Medicine
Division of Dermatology
University of California, Los Angeles
School of Medicine

REFERENCES

1. Gobbling turkey may aid psoriasis sufferers. Med World News, Oct 13, 1967, pp 87-90
2. Benton JM, Brown PE, Church RE: The serum cholesterol in psoriasis. Lancet 1:583-584, Mar 16, 1963
3. Zackheim H, Farber E: Low-protein diet and psoriasis. Arch Dermatol 99:580-586, 1969
4. Baughman R, Sobel PR: Psoriasis, stress and strain. Arch Dermatol 103:549-609, 1971
5. Savin J: Patient's beliefs about psoriasis. Bull St. Thomas Hosp, 1970, pp 139-142

Laboratory Evaluation of Neurosyphilis

TO THE EDITOR: The article "Neurosyphilis: An Update" by Dr. Roger Simon in the January 1981 issue was excellent. One major and very important aspect of the laboratory evaluation of neurosyphilis was, however, left unmentioned. I refer to the *Treponema pallidum* hemagglutination test (so-called TPHA), also known as the MHATP (microhemagglutination *Treponema pallidum).* Increasing evidence indicates that this test will replace the more expensive FTA-ABS (fluorescent treponemal antibody absorption) test for evaluation of biological false positive results for syphilis. The only apparent drawback of the MHATP is some decrease in sensitivity in primary syphilis; under those circumstances an FTA-ABS would be indicated.

JAMES B. PETER, MD, PhD
Director, Infection Laboratories, Inc.
Los Angeles

The Prevention of Nuclear War as a Medical Priority

TO THE EDITOR: What is the role of physicians in the prevention of nuclear war? Recently, two physicians approached the organized medical community with this question. Speaking before the Board of Trustees of the American Medical Association, Howard Hiatt, MD, Dean of the Harvard School of Public Health, suggested that "Talk of the use of nuclear weapons is a kind of epidemic . . . but with the term epidemic stretched beyond any meaning previously known."[1] Roger Bulger, MD, President of the University of Texas Health Sciences Center in Houston, wrote in the September 12, 1980, issue of the *Journal of the American Medical Association* that ". . . we as physicians have the obligation to transmit to our fellow citizens the nature of the effects of a nuclear war on us and the whole human race."[2]

Eighteen years ago, a group of physicians took up this question and published an article entitled "The Medical Consequences of Thermonuclear War," in the *New England Journal of Medicine.*[3] The introduction reminded readers that ". . . there are some situations in which prevention is the only effective therapy. It is hoped that readers . . . will be stimulated to play a greater part in the search for peaceful alternatives to thermonuclear war."

If physicians should accept a role in the prevention of this ultimate medical catastrophe, it is then necessary to consider factors that either increase or decrease the likelihood of nuclear war. It is here that the organized medical community has traditionally declined to become involved, observing that these considerations are outside the boundary of medical expertise. I would like to suggest that in several critical areas medical expertise can make an important contribution. These areas include the following:

- The need to estimate the injury, death and disease that result from nuclear detonations.
- The need to estimate the likelihood of accidental nuclear war due to the failure of technology and technology control.
- The need to estimate the likelihood of intentional nuclear war initiated by psychologically disturbed persons.

A recent *Scientific American* inquiry suggests that a serious underestimation exists among some military analysts of the destructive effects of nuclear weapons on health and the environment.[4] This error may have led to the formulation of the new strategy of limited nuclear war. The effects of such a limited exchange may be far greater than realized and may lower the risk threshold for all-out nuclear war.[5]

The editors of *The New York Times* were recently alarmed by the failure of an electronic circuit (worth 46 cents) at the Strategic Air Command that twice led to the incorrect perception of a Soviet nuclear attack within a three-day period.[6] As physicians familiar with machinery upon which life depends we are cognizant of the potential for failure often inherent in complex systems. We are all aware of the occasional morbidity and mor-

tality secondary to the malfunction of hardware such as respirators and heart-lung bypass devices. And we are all familiar with the rare but occasional failure of the well-trained operators of such equipment. Whereas in our medical practice technological malfunction may affect the health of one patient, in the arena of the command and control of nuclear weapons it may lead to global holocaust.

Finally, as physicians and scientists, we recognize the potential for the best of planning to be sabotaged by disturbed persons. A glance at any daily newspaper informs us of the prevalence of this instability, too often present in the leaders of certain developing nations. It is thus most disturbing to know that the international availability of nuclear fuels for electricity generation is leading to the soon irreversible proliferation of nuclear weapons.[7]

It is quite likely that a medical contribution would result in an increased appreciation of the medical damage from nuclear detonations and an increased appreciation of the likelihood of nuclear war due to technological error or psychological aberration. This could be an invaluable contribution to the deliberations of policy makers who wish to increase the security of our country and the security of the world.

I strongly urge that the medical profession as a whole consider the question of physicians' role in the prevention of nuclear war. The continued evolution of our civilization, our science and our grandchildren may await our timely answer.

HOWARD KORNFELD, MD
Program Director
Physicians for Social Responsibility, Inc.
San Francisco Bay Area Chapter
Berkeley, California

REFERENCES

1. Almost unthinkable thoughts (Editorial). Am Med News 23: 4, Aug 22, 1980
2. Bulger RJ: A physician considers nuclear war. JAMA 244: 1255, Sep 12, 1980
3. Ervin FR, Sidel VW, et al: The medical consequences of thermonuclear war. N Engl J Med 266:1126-1145, May 31, 1962
4. Lewis KN: The prompt and delayed effects of nuclear war. Sci Am 241:35-47, Jul 1979
5. The new nuclear strategy and its perils (Editorial). New York Times, Aug 22, 1980
6. That nuclear alarm wasn't false (Editorial). New York Times, Jun 30, 1980
7. Lovins AB, Lovins LH, Ross L: Nuclear power and nuclear bombs, *In* Foreign Affairs. New York City, Council on Foreign Relations, Summer, 1980, pp 1137-1177. (Recently expanded in Lovins AB, Lovins LH: Energy/War—Breaking the Nuclear Link. San Francisco, Friends of the Earth Books, 1980)

HAFE in Nepal

To the Editor: I enjoyed very much the correspondence regarding high altitude flatus expulsion (HAFE) in the February 1981 issue.[1] It brought back memories of service in Nepal. In the late 1960's problems began to appear as climbers were flown by helicopter, with very rapid gain in altitude, from the relatively low Kathmandu to high-level staging areas for assaults on major peaks. During these flights the HAFE phenomenon caused a number of unpleasant discussions and one colon rupture. When we discussed this with expedition guides we found that the problem had been long recognized. We published our findings in 1972, in the *Kathmandu Medical Bulletin,* in the article "Flatulence Accompanying Rigorous Trekking."

E. Y. DAVIS, FRCP (Ret)
Los Altos, California

REFERENCE

1. Auerbach P, Miller YE: High altitude flatus expulsion (HAFE) (Correspondence). West J Med 134:173-174, Feb 1981

Hypophosphatemia: Correct Quantity of 50 Percent Magnesium Sulfate

To the Editor: I am writing in regard to the fine review of hypophosphatemia by Dr. James P. Knochel which appeared in the January issue.[1] The article was very well written and well referenced, and gave very useful and timely advice on management of the condition. Unfortunately, the last paragraph of text contains a serious error of potentially great clinical significance: a solution is discussed that contains, among other components, "20 ml of 50 percent magnesium (16 mEq of magnesium)." However, 20 ml of 50 percent magnesium sulfate contains 80 mEq of magnesium, not 16. The administration of the stated solution three times a day for several days could conceivably lead to symptomatic magnesium intoxication.

I feel that every effort should be made to correct this error for the journal's readers because many people will want to employ Dr. Knochel's recommendation.

WILLIS C. TRIPLETT, PharmD
Clinical Pharmacist
Methodist Hospital of Indiana, Inc.
Indianapolis

REFERENCE

1. Knochel JP: Hypophosphatemia (Nutrition in Medicine). West J Med 134:15-26, Jan 1981

* * *

Dr. Knochel Replies

To the Editor: In my review "Hypophosphatemia" an error was made for the dosage of 50 percent magnesium sulfate ($MgSO_4 \cdot 7H_2O$). The correct quantity of 50 percent magnesium sulfate that should be administered intravenously is 4 ml every eight hours. This volume contains 16 mEq of magnesium. My gratitude is extended to Dr. Triplett for recognizing this error.

JAMES P. KNOCHEL, MD
Chief, Medical Service
Veterans Administration Medical Center
Dallas

Refer to: Maron DJ: Preventive medicine in practice: The state of the art (From a Medical Student). West J Med 134: 367-372, Apr 1981

From a Medical Student

Preventive Medicine in Practice: The State of the Art

DAVID J. MARON, BA, *Beverly Hills, California*

Primary and secondary prevention, as opposed to tertiary prevention, is the logical approach to attack today's leading causes of premature death. To apply preventive medicine in their practices, physicans may use a number of tools. The traditional annual examination should be abandoned in favor of periodic screening of asymptomatic patients according to age and sex. Screening should be done on a case-finding basis, facilitated by use of a longitudinal screening flow sheet and evaluated by use of a retrospective audit. An age-sex register can help identify which patients belong to a high-risk group. Health hazard appraisal is a tool for estimating a patient's risk before and after prescribed preventive intervention, and may stimulate patient risk factor reduction —as may other behavior modification techniques. In many cases these tools can be applied by paramedical personnel. Further research is needed to gauge the effects of these techniques on risk, morbidity and mortality.

DESPITE THE increasing interest in recent years in preventive medicine, there has been a lag in development of a sound, scientific basis for its practice.[1] It is the purpose of this article to examine the present state of the art of preventive medicine, with particular emphasis on the role of primary care physicians and asymptomatic adult patients.

Preventive medicine may be typed as primary, secondary or tertiary.[2] Primary prevention is the prevention of any clinical manifestations of disease—that is, health maintenance and health promotion. Secondary prevention is the early detection and treatment of established disease in an asymptomatic person. Tertiary prevention is the rehabilitation, palliation and avoidance of further complications in a person with symptomatic illness. Traditionally, clinical medicine has taken the form of tertiary prevention. The term preventive medicine in this article refers only to primary and secondary prevention, meaning both action taken to ward off the development of signs and symptoms of disease in people who are at risk, and action to promote health. Primary care refers to first-contact and continuing general care by a physician who assumes the role of coordinating overall patient management[3] and delivering comprehensive health care.[4]

Since the turn of the century heart disease, cancer and stroke have replaced infectious diseases as the leading causes of death. Research over the last few decades has provided us with an improved

Mr. Maron is a fourth-year medical student, class of 1981, University of Southern California School of Medicine, Los Angeles.

Reprint requests to: Mr. David J. Maron, 609 North Linden Drive, Beverly Hills, CA 90210.

understanding of the natural history of these modern diseases. It has been found that the precursors—or risk factors that predispose persons to having these problems develop—are largely linked to life-style patterns. Belloc examined seven personal health-promoting practices and found that the number observed was positively correlated with physical health status and negatively correlated with mortality.[5]

The United States Department of Health, Education, and Welfare published the first Surgeon General's Report on Health Promotion and Disease Prevention with the intention "to encourage a second public health revolution in the history of the United States."[6] It cited cigarette smoking as the "single most important preventable cause of death." Cigarette smoking is a major risk factor for cardiovascular disease, the number one cause of death, and it is responsible for approximately 80 percent of all lung cancer, the most common form of cancer in men. According to the report, alcohol is responsible for more than 10 percent of all deaths in this country. Cirrhosis is the seventh leading cause of death in the United States,[7] and 95 percent of deaths from this cause are alcohol related.[6] About 50 percent of drivers fatally injured in car accidents have been found to have elevated blood alcohol levels. An estimated 80 percent of Americans do not use lap or shoulder seat belts while driving. Occupational hazards may be associated with 20 percent of total cancer mortality. In summary, the document estimates that "as much as half of U.S. mortality in 1976 was due to unhealthy behavior or life-style."[6] Thus, the leading causes of premature death are preventable. It is also apparent that traditional medicine, which focuses on the diagnosis and treatment of overt disease, is not an adequate approach to reducing premature death and promoting health.

Preventive medicine is clearly indicated, and could take many alternative forms. One mode, which is the topic of this article, is the practice of preventive medicine within the individual doctor-patient relationship: the medical model. If primary care physicians are responsible for delivering comprehensive health care, then this includes the responsibility for prolonging useful life expectancy by protecting patients from diseases for which signs and symptoms have not yet appeared.[4]

Many other modes of primary and secondary prevention exist. The use of mass media has proved to be an effective tool in lowering disease risk.[8] The use of peer leaders as the primary agents of intervention show promising short-term results in the learning of pressure-resistance skills in adolescents.[9] Indeed, there is a multitude of public health policies that, if implemented, could contribute greatly to preventing disease. It is beyond the scope of this paper to expose these other possibilities. Rather, this paper focuses only on certain office techniques that primary care physicians can use to apply the principles of preventive medicine.

Periodic Health Examinations

Preventive medicine differs from traditional medicine in that physicians, and not patients, initiate the intervention.[1] As opposed to a symptomatic patient, an apparently healthy, asymptomatic person rarely asks for the services of a physician. In preventive medical practice, a physician is the prime mover with the application of screening procedures. Screening is defined as "the presumptive identification of unrecognized disease or defect by the application of tests, examinations, or other procedures which can be applied rapidly."[10] The tendency of primary care practitioners in the United States has been to carry out mass, multiphasic screening annually for each asymptomatic person older than 5 years of age, without evidence that this ritual is either effective in changing the outcome of many diseases or is an economically justifiable use of existing medical resources.[11]

Frame and Carlson[1] developed a program for primary care physicians to conduct periodic health screening of asymptomatic adults. They proposed specific screening criteria and suggested the use of a longitudinal screening flow sheet to aid identification of what examinations or tests should be done at what intervals for which asymptomatic patients. Breslow and Somers[12] made an effort to "construct a lifetime schedule, or series of 'packages' of effective individual preventive procedures as an alternative to the annual checkup." They divided the life span into ten periods, based on changing life-styles, health needs and problems. For each period, they formulated a set of overall health goals and professional services or requirements related to these goals. They also suggested eight criteria for the selection of a screening procedure:

(1) the procedure is appropriate to the health goals of the relevant age group (or groups) and is acceptable to

the relevant population; (2) the procedure is directed to primary or secondary prevention of a clearly identified disease or condition that has a definite effect on the length or quality of life; (3) the natural history of the disease (or diseases) associated with the condition is understood sufficiently to justify the procedure as outweighing any adverse effects of intervention; (4) for purposes of screening, the disease or condition has an asymptomatic period during which detection and treatment can substantially reduce morbidity or mortality or both; (5) acceptable methods of effective treatment are available for conditions discovered; (6) the prevalence and seriousness of the disease or condition justify the cost of intervention; (7) the procedure is relatively easy to administer, preferably by paramedical personnel with guidance and interpretation by physicians, and generally available at reasonable cost; and, (8) resources are generally available for follow-up diagnostic or therapeutic intervention if required.

The Canadian Task Force on the Periodic Health Examination was established in 1976 to evaluate the merits of traditional checkups and to make recommendations.[13] Its goal was to "recommend a plan for a lifetime program of periodic health assessment" to enhance or protect the health of the population. The final recommendation of the committee was that "the routine annual checkup be abandoned in favor of a selective approach that is determined by a person's age and sex." They created 18 health protection packages "to be performed at 35 specified times between conception and old age . . . appropriate to the various health needs at the different stages of human life." Their recommendations represent minimum standards for asymptomatic persons at risk. A five-year interval was arbitrarily selected as the average time between checkups for the nonpregnant adult up to the age of 74. The interval chosen was arbitrary because there is "virtually no evidence about the optimal frequency of most of the components of the packages." A two-year interval was recommended for those 75 years old or older. Furthermore, the report recommended that the periodic health packages be used for case-finding rather than screening; in other words, screening patients already visiting a doctor's office for symptomatic complaints, rather than specifically scheduling an appointment solely for screening purposes. (Exceptions to this recommendation are for prenatal care, well-child care and geriatric care.) The task force suggested that primary care physicians record a cumulative checklist of screening maneuvers to facilitate case-finding screening. Age-sex registers were recommended in order to aid community-based research about the effectiveness of periodic health examinations. Such a register could also help to readily identify high-risk patient subgroups for whom a preventive intervention may be appropriate.

Frame[11] advocates the use of a retrospective performance audit to evaluate how well screening is being implemented.

Eddy[14] reviewed several clinical and epidemiologic studies and, applying screening criteria similar to those of Breslow and Somers, made recommendations about tests for the early detection of cancer; these recommendations have been adopted by the American Cancer Society. A cancer-related health checkup is recommended every three years for all persons over 20, and every year for all persons over 40.

Recommendations from the American Cancer Society and other sources about the use of certain screening tests in asymptomatic adults are summarized in Table 1. Most of these recommendations are based on nonrandomized or uncontrolled trials and clinical judgment,[14] which explains the striking variety of proposed screening schedules. Unable to await more precise data, physicians should act with the best available information—even though it is incomplete. Individual physicians should choose the protocol consistent with (1) their interpretation of the available data, (2) the individual risk factors of a patient and (3) the objectives and budget of a patient. The desire to provide the best care possible may lure a clinician into using unjustifiably frequent or inappropriate screening tests without proper consideration of associated risks, side effects, or monetary and nonmonetary costs to the patient and society. Furthermore, if the projected oversupply of physicians in this country becomes a reality, the financial incentive to provide screening tests may become an increasingly difficult barrier to the responsible practice of preventive medicine.

Health Hazard Appraisal

In 1968 Sadusk and Robbins[4] introduced health hazard appraisal (HHA) as a technique for outlining a preventive medicine program in comprehensive health care by primary care physicians. HHA is based upon the fact that every person possesses certain quantifiable health hazards as a member of a sex-age-race constituted group, and that these average risks may be applied to the individual patient if the physician knows the patient's prognostic characteristics and the mortality experience of cohorts with similar prognostic characteristics. Consequently, with knowledge of

a patient's clinical, historical and life-style data, a clinician can apply risk multipliers to baseline risks to compute (1) the patient's risk of death in an ensuing ten-year period, (2) the appraisal age, which reflects the overall measure of risk and (3) the compliance age, which reflects the reduced total risk if the patient complies with a set of recommended preventive interventions. Only the leading 10 to 15 causes of death are chosen for risk estimation, and attention is paid only to those risk factors that have the greatest probability of affecting a person's health.[15]

HHA is the prototype upon which other risk appraisal instruments have been formed.[16] Implied in all methods of risk estimation is that information in addition to the typical history and physical examination must be obtained. In-depth histories are necessary, including such information as occupational hazards, cigarette and alcohol use, use of other drugs, number of miles driven per year, use of seat belts, diet patterns, level of activity, possession of dangerous weapons and ability to manage stress. Such information can be obtained by paramedical personnel.

Risk Factor Reduction

The usefulness of HHA is predicated on two assumptions:[16] (1) giving persons information about their own risk will lead to actions perceived as and directed at reducing risk and (2) given a particular disease with a known incidence and for which there are identified risk factors, then reducing risk in an individual patient will indeed lead to a lower probability that the disease will develop. In attempting to substantiate these hypotheses, it is important to update the information regarding changes in prevalence, morbidity incidence, mortality (with geographic variation) and risk reducibility, as well as to update the models for estimating risk. A few studies using HHA in conjunction with patient counseling as a tool to reduce risks have been reported.[17-20] These studies

TABLE 1.—*A Summary of Recommendations From Different Sources About the Use of Certain Screening Procedures to Detect Different Types of Conditions in Asymptomatic Persons*

Test or Procedure	*Age and Frequency*
Pap smear	
ACOG	Initial smear when sexually active or age 18. Repeat in six months, then annually.
Frame	Initial smear when sexually active or age 21. Repeat in one year, then every two years.
ACS	Initial smear when sexually active or age 20. Repeat in one year, then every three years to age 65. More frequently in high-risk women.
CTF	Initial smear when sexually active. Repeat in one year, then every three years to age 35 and every five years thereafter. Annual smears in high-risk women.
Stool occult blood test	
Frame	Every two years between ages 40 and 50, then annually.
ACS	Annually over age 50.
CTF	Not more frequently than annually over age 45.
Sigmoidoscopy	
Frame	Not routinely recommended; single procedure age 55.
ACS	Initial procedure over age 50, repeat in one year, then every three to five years.
CTF	Not recommended.
Digital rectal examination	
Frame	Not recommended.
ACS	Annually over age 40.
CTF	Not recommended.
Breast self-examination	
F and C	Every month, starting at age 20.
ACS	Every month over age 20.
CTF	To be researched.
Breast physical examination	
F and C	Every two years between the ages 20 and 50, then annually.
ACS	Every three years between the ages 20 and 40, then annually.
CTF	Annually between the ages 50 and 59.
Mammography	
F and C	Annually or biannually only in women over 50 with large, fatty breasts.
ACS	Baseline between the ages 35 and 40. Consult personal physician under age 50. Annually over age 50.
CTF	Annually between the ages 50 and 59.
Chest x-ray	
F and C	Not recommended.
ACS	Not recommended.
CTF	Not recommended.
B and S	Not recommended.
Electrocardiogram	
F and C	Not recommended.
CTF	Not recommended.
B and S	Every five years over age 40.
Serum cholesterol	
F and C	Every four years in all adults.
CTF	Not recommended other than once to screen young males for hyperlipidemia.
B and S	Every five years over age 40.

ACOG = American College of Obstetricians and Gynecologists[11]
ACS = American Cancer Society[14]
B and S = Breslow and Somers[12]
CTF = Canadian Task Force[13]
F and C = Frame and Carlson[1]
Frame[11]

suggest that HHA is effective in stimulating risk reduction. However, Sacks and co-workers[20] evaluated the reliability of the HHA questionnaire and found a high degree of inconsistency in the responses to a baseline questionnaire compared with a follow-up questionnaire. The study concluded that the reliability of the HHA questionnaire is questionable, and that the previously reported successes of HHA in stimulating risk reduction may only reflect the variation in response when a person fills out the questionnaire twice. Before this tool is adopted into widespread practice or accepted as a reliable longitudinal measure of risk, randomized controlled trials must be done to study the issue of reliability in addition to reduction in risk, morbidity and mortality.

Even if carried out according to the most thoughtful criteria, a physician does a questionable service by screening and appraising the health of a patient only to terminate the encounter with advice such as "quit smoking" or "lose weight." Such a method has a poor success rate.[21] Although education is a necessary step toward risk factor reduction, it alone is rarely sufficient.[9] How to make it most probable that a patient will indeed improve his or her life-style patterns is the most difficult challenge of preventive medicine.

The behavioral sciences supply both the theoretical framework for understanding the origins of behavior and the methods for achieving self-directed change. Bandura developed a theory of social learning which discusses the source of behavior patterns in the context of role models, antecedent determinants (stimuli) and consequent determinants (reinforcers) of personal action.[22] His theory provides a basis for understanding the mechanism of behavior change. Work by other behavioral scientists has led to specific techniques for achieving changes in attitude and behavior.[23] Examples of such techniques include setting realistic goals; showing commitment to change by signing contracts to reach these goals; enlisting emotional support from family and friends; recording in a diary the context, frequency and other features of the problem behavior; learning to talk to oneself to counter those attitudes that are barriers to adopting change, and learning to reward oneself for positive changes.

It is feasible for primary care physicians to use the principles of behavior modification in their office practices. This may be realistically achieved by using the talents of another health provider—such as a nurse, nurse practitioner, physician's assistant or health educator—who has acquired expertise in behavior modification techniques. Unfortunately, there are few data available to evaluate the effectiveness of this approach.

Summary

The leading causes of premature death are related to life-style and are therefore preventable. However, traditional medicine, which focuses on the diagnosis and treatment of overt disease, does not meet the challenge that these modern diseases present. Primary and secondary prevention is the logical approach to improve our country's health status. Yet the growth in interest in preventive medicine has not been accompanied by an equally strong development of a sound, scientific approach to its clinical practice.

This article has not discussed all of the various effective methods of preventive intervention, but only explores the practice of prevention within the medical model. The physicians' role within this model has been proposed by Lichtenstein and Danaher,[21] Robbins and Hall,[15] Schuman[24] and others.[1,4] A synthesis of their views is as follows: (1) act as a model of a healthy life-style, (2) detect risk using proved screening tools, (3) provide information clarifying the risk associated with the habit, and the risk reduction if the patient stops, (4) encourage life-style change by direct advice and suggestions, and by the use of behavior modification techniques whenever possible, (5) refer the patient to a specialized program if necessary, (6) prescribe and follow up the use of specific behavioral change and maintenance strategies and (7) keep track of successes and failures, and revise the strategy accordingly.

In attempting to fulfill this role physicians are faced with a difficult task. From this review it is painfully clear that virtually any preventive technique for use on asymptomatic adults is based upon incomplete data. We do not have the evidence from randomized, controlled trials that the tools described—periodic health examinations, HHA and risk factor reduction techniques—are effective in reducing risk, morbidity and mortality. Clinicians must act today based on the best available data. (Ironically, the primary care implementation of these tools may provide valuable information regarding their effectiveness.) Using presently available data, the following are practical suggestions for primary care providers of preventive medicine.

Many screening tests or procedures in wide-

spread use on asymptomatic adults should be reduced in frequency of application if not discarded. The author agrees with Hulley and associates[25] that "active intervention should not be pursued in the general practice of preventive medicine until there is persuasive evidence, not just that the action will do no harm, but that it will be beneficial." The desire to provide the best possible medical care, to follow "common practice," intuition or personal emotional bias, and the presence of strong financial incentives to provide screening tests, are powerful forces that run counter to scientific judgment. It is understood that different persons may quite properly elect to interpret the available information differently or to place different importance upon the expected benefits, risks and costs of intervention.[14] Nevertheless, thoughtful criteria for the application of screening tests have been proposed and demand recognition.

Traditional annual examinations should be abandoned in favor of periodic screening according to age and sex. Screening should be done on a case-finding basis—that is, during visits for other symptomatic complaints. Development of a longitudinal screening flow sheet for asymptomatic adults is recommended[1,11,13,26] as a valuable tool to check to see if screening is needed at every patient visit, and a retrospective audit can help to evaluate the implementation of a screening program.[11]

The development of an age-sex register may help physicians to easily identify which patients are members of a high-risk group for a specific disease, in the event that a new screening test, immunization or the like should become available.

The incorporation of major risk factors into a patient's problem-oriented medical record and problem list may help a clinician assess the overall risk for a given patient and allow for monitoring over time. However crude the instrument for assessing risk, it is necessary to elicit information in a history that might not ordinarily be considered to lie within the realm of conventional medicine. The HHA questionnaire may prove to be a valuable tool, but further research to establish it as such is necessary. The use of paramedical personnel—such as nurses, nurse practitioners, physician's assistants or health educators—should be considered for applying preventive techniques within an office practice.

Further research is necessary to both update the tools of the medical model of preventive medicine and to evaluate the effectiveness of this model compared with other approaches to primary and secondary prevention.

REFERENCES

1. Frame PS, Carlson SJ: A critical review of periodic health screening using specific screening criteria. J Fam Pract 2:29-36: 123-129, 189-194, 283-289, 1975

2. Berg AO: Prevention in perspective: History, concepts, and issues. J Fam Pract 9:37-46, Jul 1979

3. Stewart MM: Primary care in the large urban hospital, *In* Nobel J (Ed): Primary Care and the Practice of Medicine. Boston, Little, Brown and Co., 1976, pp 209-227

4. Sadusk JF, Robbins LC: Proposal for health-hazard appraisal in comprehensive health care. JAMA 203:1108-1112, Mar 1973

5. Belloc NB: Relationship of health practices and mortality. Prev Med 2:67-81, Mar 1973

6. Healthy People. US Department of Health, Education, and Welfare, 1979

7. Vital Statistics Los Angeles County 1977. County of Los Angeles, Department of Health Services, 1979

8. Farquhar JW, Maccoby N, Wood PD, et al: Community education for cardiovascular health. Lancet 1:1192-1195, Jun 4, 1977

9. McAlister AL, Perry C, Maccoby N: Adolescent smoking: Onset and prevention. Pediatrics 63:650-658, Apr 1979

10. Froom J, Boisseau V, Sherman A: Selective screening for lead poisoning in an urban teaching practice. J Fam Pract 9: 65-70, Jul 1979

11. Frame PS: Periodic health screening in a rural private practice. J Fam Pract 9:57-64, Jul 1979

12. Breslow L, Somers AR: The lifetime health-monitoring program—A practical approach to preventive medicine. N Engl J Med 296:601-608, Mar 17, 1977

13. The Task Force on the Periodic Health Examination: Periodic (vs. annual) health examination. Can Med Assoc J 121: 1-45, Nov 3, 1979

14. Eddy D: Guidelines for the cancer-related checkup—Recommendations and rationale. CA 30:194-240, Jul-Aug 1980

15. Robbins LC, Hall JH: Prospective medicine, *In* Rakel RE (Ed): Family Practice, 2nd Ed. Philadelphia, WB Saunders, 1978, pp 160-174

16. Goetz AA, Duff JF, Bernstein JE: Health risk appraisal: The estimation of risk, *In* National Conference on Health Promotion—Programs in Occupational Settings, State-of-the-Art Papers. Office of Health Information and Health Promotion, Office of the Assistant Secretary for Health, US Department of Health, Education, and Welfare, Jan 1979

17. LaDou J, Sherwood JN, Hughes L: Health hazard appraisal in patient counseling. West J Med 122:177-180, Feb 1975

18. LaDou J, Sherwood JN, Hughes L: Health hazard appraisal counseling—Continuing evaluation. West J Med 130:280-285, Mar 1979

19. Rodnick JE, Bubb K: Patient education and multiphasic screening: It can change behavior. J Fam Pract 6:599-607, 1978

20. Sacks JJ, Krushat WM, Newman J: Reliability of health hazard appraisal. Am J Public Health 70:730-732, Jul 1980

21. Lichtenstein E, Danaher BG: What can the physician do to assist the patient to stop smoking? *In* Brashear RE, Rhodes ML (Eds): Chronic Obstructive Lung Disease: Clinical Treatment and Management. St. Louis, CV Mosby, 1978, pp 227-241

22. Bandura A: Social Learning Theory. Englewood Cliffs, NJ, Prentice Hall, 1977

23. Farquhar JW: The American Way of Life Need Not be Hazardous to Your Health. New York, WW Norton and Co, 1978

24. Schuman SH: Prevention: The vital and unique role of the family physician. J Fam Pract 9:97-102, Jul 1979

25. Hulley SB, Rosenman RH, Bawol RD, et al: Epidemiology as a guide to clinical decisions—The association between triglyceride and coronary heart disease. N Engl J Med 302:1383-1389, Jun 19, 1980

26. Sloane P: A prevention oriented medical record. J Fam Pract 9:89-96, Jul 1979

NEVADA STATE MEDICAL ASSOCIATION

77th annual meeting

CARSON CITY • MAY 14-17, 1981 • ORMSBY HOUSE

scientific session

MAY 15, 1981

CME POTPOURRI

Morning Session

8:00 DUODENAL ULCER DISEASE—SURGERY
ROBERT S. PETERS, MD, FACP, Associate Chief of Medicine
Director of Gastroenterology, Valley Hospital, Fresno, CA

9:10 DIAGNOSIS AND MANAGEMENT OF THE SOLITARY THYROID NODULE
ERNEST MAZZAFERRI, MD, Chairman of Department of Medicine
University of Nevada-Reno Medical School

10:20 Refreshment Break

10:40 HEPATIC ARTERY INFUSION
SAMUEL SPIVACK, MD, Associate Clinical Professor of Medicine
University of California, San Francisco

Noon **JOINT NSMA/AUXILIARY LUNCHEON**
Speaker: Nevada Attorney General RICHARD BRYAN

Afternoon Session

1:30 CEREBROVASCULAR DISEASE—NATURAL HISTORY VS. SURGICAL ALTERNATIVES
JOHN THOMAS MEHIGAN, MD, Assistant Clinical Professor, Stanford University Hospital

2:45 Refreshment Break

3:10 SEXUALLY TRANSMITTED DISEASES—THE BIG FOUR—1981
MICHAEL APICELLA, MD, Director of Division of Infections Diseases
University of Nevada-Reno Medical School

4:30 CLOSING REMARKS AND ADJOURNMENT
WILLIAM THOMAS, MD, Program Director

Approved for Category I Hours (AMA and AAFP)

Registration for Scientific Session only

MEMBERS $75 ($80 AT DOOR) • NONMEMBERS $125 ($130 AT DOOR) • LUNCHEON $10 PER PERSON

For registration material contact

Nevada State Medical Association, 3660 Baker Lane, Reno, NV 89509 • (702) 825-6788

NEW MEXICO MEDICAL SOCIETY ANNUAL MEETING

HILTON INN

ALBUQUERQUE, NEW MEXICO

MAY 6-8, 1981

CRITICAL CARE FOR THE COMMUNITY HOSPITAL

DEFINITIONS:	
What Is Critical Care?	JAMES FORRESTER, MD, Department of Cardiology, Cedars-Sinai Medical Center, Los Angeles
Appropriate and Inappropriate Care for Different Communities	MARK SIEGLER, MD, Department of Medicine, University of Chicago, Pritzker School of Medicine
SPECIFIC PROBLEMS:	
The First Thirty Minutes	ROBERT C. HENRY, MD, Emergency Department, Presbyterian Hospital, Albuquerque
The Patient with an Arrhythmia	BARRY RAMO, MD, Coronary Care Unit, Presbyterian Hospital, Albuquerque
Hypertensive Crisis	RICHARD GOLDMAN, MD, Department of Nephrology, University of New Mexico School of Medicine, Albuquerque

SCIENTIFIC SESSION

Children in Respiratory Distress	ROGELIO MENENDEZ-CORDOVA, MD, Department of Pediatrics, University of New Mexico School of Medicine, Albuquerque
The Adult Patient in Respiratory Distress	THOMAS W. CHICK, MD, Pulmonary Function Laboratory, Veterans Administration Medical Center, Albuquerque
Symposium on Shock—Cardiogenic	FRANK MOWRY, MD, Cardiovascular Diseases, Albuquerque
Septic	U. G. HODGIN Jr, MD, Internal Medicine, Albuquerque
Hemorrhagic	JOHN N. WILSON, MD, Thoracic and Cardiovascular Surgery, Albuquerque
Acute Psychosis	ROBERT KELLNER, MD, Department of Psychiatry, University of New Mexico School of Medicine, Albuquerque
ETHICAL PROBLEMS OF CRITICAL CARE:	
Are there patients who should not be resuscitated?	JAMES FORRESTER, MD
The unconscious patient—when may life support be terminated?	MARK SIEGLER, MD
How to establish an effective hospital ethics committee.	GEORGE M. BOYDEN, MD, Medical Director, Presbyterian Hospital, Albuquerque

REGISTRATION FORM

Name _____ Phone _____

Address _____ Zip _____

Member—$30.00 before May 1, thereafter $35.00
Nonmember—$50.00 Interns, Residents, Government Service $10.00
Medical Students, Nurses, Emeritus Members—fee waived

☐ Check enclosed

Make checks payable to and mail to: NEW MEXICO MEDICAL SOCIETY
P.O. Box 9366
Albuquerque, NM 87119

in memoriam

California Medical Association

ALBRECHT, JOHN GEORGE, Los Gatos. Died January 21, 1981 in Monte Serono of myocardial infarct, aged 51. Graduate of the University of Maryland School of Medicine, Baltimore, 1955. Licensed in California in 1959. Dr. Albrecht was a member of the Santa Clara County Medical Society.

BEARE, WILLIAM KELLER, San Rafael. Died February 2, 1981 in San Rafael of cerebrovascular accident, aged 80. Graduate of Washington University School of Medicine, St. Louis, 1933. Licensed in California in 1934. Dr. Beare was a member of the Marin Medical Society.

BELL, H. GLENN, San Francisco. Died January 28, 1981 in Daly City of cerebrovascular accident, aged 87. Graduate of the University of Cincinnati College of Medicine, 1923. Licensed in California in 1929. Dr. Bell was a retired member of the San Francisco Medical Society.

ECKARDT, DAVID L., Beverly Hills. Died February 5, 1981, aged 37. Graduate of the University of Florida College of Medicine, Gainesville, 1969. Licensed in California in 1972. Dr. Eckardt was a member of the Los Angeles County Medical Association.

GILBERT, JACK C., Cedarville. Died in Cedarville of cancer, aged 61. Graduate of Hahnemann Medical College and Hospital of Philadelphia, 1950. Licensed in California in 1951. Dr. Gilbert was a member of the Lassen-Plumas-Modoc-Sierra County Medical Society.

GLYER, C. HARTLEY, Mountain View. Died February 9, 1981 in Mountain View, aged 66. Graduate of Northwestern University Medical School, Chicago, 1940. Licensed in California in 1940. Dr. Glyer was a member of the Santa Clara County Medical Society.

HEMINGWAY, THOMAS F., Sacramento. Died January 18, 1981 in Utah, aged 64. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1947. Licensed in California in 1947. MD degree from California College of Medicine, 1962. Dr. Hemingway was a retired member of the Sacramento-El Dorado Medical Society.

HOAGLAND, PAUL I., Pasadena. Died January 29, 1981, aged 68. Graduate of the Stanford University School of Medicine, Palo Alto-San Francisco, 1938. Licensed in California in 1938. Dr. Hoagland was a retired member of the Los Angeles County Medical Association.

JOHNSON, OSCAR F., Sacramento. Died January 16, 1981 in Sacramento, aged 81. Graduate of the Stanford University School of Medicine, Palo Alto-San Francisco, 1919. Licensed in California in 1919. Dr. Johnson was a retired member of the Sacramento-El Dorado Medical Society.

JOHNSTON, RUSSELL CONRAD, Santa Rosa. Died February 3, 1981 in Wellington, New Zealand of myocardial infarct, aged 72. Graduate of Northwestern University Medical School, Chicago, 1934. Licensed in California in 1934. Dr. Johnston was a member of the Sonoma County Medical Association.

KEMP, GEORGE L., Laguna Hills. Died November 16, 1980, aged 53. Graduate of Des Moines Still College of Osteopathy, Des Moines, 1953. Licensed in California in 1956. MD degree from California College of Medicine, 1962. Dr. Kemp was a member of the Orange County Medical Association.

KLOSS, RICHARD G., Placerville. Died December 30, 1980 in Oregon of injuries received in automobile accident, aged 74. Graduate of the University of California Medical School, Berkeley-San Francisco, 1940. Licensed in California in 1940. Dr. Kloss was a member of the Sacramento-El Dorado Medical Society.

LAWRY, EDWIN V., Palo Alto. Died February 8, 1981 in Palo Alto, aged 71. Graduate of Cornell University Medical College, New York, 1935. Licensed in California in 1937. Dr. Lawry was a retired member of the Santa Clara County Medical Society.

LOWE, FRANK A., San Francisco. Died February 7, 1981 in San Francisco, aged 90. Graduate of the College of Physicians and Surgeons, Medical Department, University of Southern California, Los Angeles, 1915. Licensed in California in 1915. Dr. Lowe was a retired member of the Marin Medical Society.

MERRYMAN, GEORGE H., Kentfield. Died January 18, 1981, aged 68. Graduate of the University of Oregon Medical School, Portland, 1938. Licensed in California in 1946. Dr. Merryman was a retired member of the Marin Medical Society.

OIER, GEORGE W., Sonoma. Died December 28, 1980 in Oakland of cancer, aged 64. Graduate of the University of California Medical School, Berkeley-San Francisco, 1943. Licensed in California in 1943. Dr. Oier was an associate member of the Napa County Medical Society.

PRATT, BENJAMIN H., Lemoore. Died January 18, 1981 in Tracy, aged 92. Graduate of the University of California Medical School, Berkeley-San Francisco, 1922. Licensed in California in 1922. Dr. Pratt was a retired member of the Kings County Medical Society.

STRUBLE, HOMER P., Hayward. Died January 4, 1981, aged 80. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1926. Licensed in California in 1926. Dr. Struble was a member of the Alameda-Contra Costa Medical Association.

STURR, ROBERT P., JR., Long Beach. Died July 4, 1980, aged 56. Graduate of Jefferson Medical College, Philadelphia, 1948. Licensed in California in 1960. Dr. Sturr was a member of the Los Angeles County Medcial Association.

TEDFORD, JOHN A., Burbank. Died June 7, 1980, aged 74. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1933. MD degree from California College of Medicine, 1962. Licensed in California in 1933. Dr. Tedford was a retired member of the Los Angeles County Medical Association.

TEVIOTDALE, JAMES R., Carpinteria. Died December 2, 1979, aged 72. Graduate of the University of Alberta Faculty of Medicine, Edmonton, 1938. Licensed in California in 1939. Dr. Teviotdale was a retired member of the Los Angeles County Medical Association.

TUCKER, JACK S., Grass Valley. Died January 4, 1981, aged 67. Graduate of the University of Kansas School of Medicine, Lawrence-Kansas City, 1936. Licensed in California in 1946. Dr. Tucker was a retired member of the Alameda-Contra Costa Medical Association.

VOLLMER, HENRY W., Loma Linda. Died February 2, 1981, aged 99. Graduate of the American Medical Missionary College, Chicago, 1905. Licensed in California in 1918. Dr. Vollmer was a retired member of the Los Angeles County Medical Association.

VON DER GROEBEN, JOBST, Tracy. Died February 7, 1981 in Tracy, aged 65. Graduate of Johann Wolfgang Goethe-Universität Medizinische Fakultät, Frankfurt-am-Main, Prussia, 1948. Licensed in California in 1950. Dr. von der Groeben was a member of the San Joaquin County Medical Society.

WEINSTEIN, MORTON H., Oakland. Died February 4, 1981 in San Francisco, aged 68. Graduate of Northwestern University Medical School, Chicago, 1936. Licensed in California in 1947. Dr. Weinstein was a member of the Alameda-Contra Costa Medical Association.

Washington State Medical Association

COLEMAN, JULIAN H., Seattle. Died February 16, 1981, aged 80. Graduate of the University of Virginia School of Medicine, Charlottesville, 1931. Licensed in Washington in 1932. Dr. Coleman was a retired member of the King County Medical Society.

HOFER, AMOS C., Seattle. Died February 7, 1981 in Seattle, aged 64. Graduate of Northwestern University Medical School, Chicago, 1943. Licensed in Washington in 1944. Dr. Hofer was a retired member of the King County Medical Society.

MCVAY, JOHN P., Seattle. Died December 25, 1980 in Seattle, aged 77. Graduate of the University of Oregon Medical School, Portland, 1932. Licensed in Washington in 1933. Dr. McVay was a retired member of the King County Medical Society.

PARKER, DEAN, Monroe. Died January 12, 1981 in Lake Havasu City, Arizona, aged 69. Graduate of the University of Iowa College of Medicine, Iowa City, 1939. Licensed in Washington in 1947. Dr. Parker was a retired member of the King County Medical Society.

SMITH, DAVID W., Seattle. Died January 23, 1981 in Seattle, aged 54. Graduate of the Johns Hopkins University School of Medicine, Baltimore, 1958. Licensed in Washington in 1968. Dr. Smith was a member of the King County Medical Society.

If the Western Journal didn't exist,

Someone would have to invent it.

The Western Journal of Medicine fills several important needs. It's an especially useful and practical journal for physicians in practice. Also, it provides unique coverage of social and economic trends affecting medicine (the current issue is a good example). And, not least important, it's a voice for medicine in the West. Medical achievements in the Western states are brought to the attention of the profession at large and communication is maintained among Western physicians.

Undoubtedly you can think of several people—a friend in another part of the country, a colleague in the West, a student—who should be receiving the *Western Journal* regularly. Why not subscribe for them? The cost is low. A year's subscription is just $10 in the United States and Canada ($18 in all other countries). If you wish, we'll send a card announcing your gift.

Please mail this coupon with enclosed payment to: WJ4/81

THE WESTERN JOURNAL OF MEDICINE — Circulation Department

731 Market Street, San Francisco, California 94103

Subscriptions: U.S. and Canada $10 All other countries $18

Enclosed is $_____ to cover _____ subscriptions.

Send subscription

TO: _____

_____

Street

_____

City State Zip

_____

Specialty

Gift Card to read "From _____"

TO: _____

_____

Street

_____

City State Zip

_____

Specialty

Gift Card to read "From _____"

Leadership

It took time to achieve it
It takes dedication to keep it

Purepac became the largest generic drug manufacturing facility in the United States by providing high quality generic pharmaceuticals at the lowest possible cost. We know that to be on top tomorrow, we've got to stay a few steps ahead today. Here are some of the steps we've already taken:

- **Full-time Medical Vice President with Supporting PhD Staff**
- **ANDA/Patent Review Departments**
- **State Formulary Manager**
- **Regulatory Affairs Department**
- **Comprehensive Advertising and Marketing Support Programs**

It took Purepac 50 years to achieve this leadership position. And we're determined to provide you with even more quality products and dedicated services in the next 50 years.

PUREPAC PHARMACEUTICAL CO.
Division of Kalipharma, Inc., Elizabeth, N.J. 07207

1930-1981

Celebrating over 50 years of industry leadership.

GN-1080

(Continued from Page 31)

PHYSICIANS WANTED

SOUTHERN CALIFORNIA REGIONAL DIRECTOR—Would prefer physician with background in either preventive or internal medicine. Expected to assume both clinical and administrative duties within corporate medical department and Southern California area. Salary commensurate with qualifications and experience. Send résumé to Reynold T. Schmidt, MD, Box 7600, Los Angeles, CA 90051.

FAMILY PRACTICE—Board certified/eligible for Ambulatory Care Department of Merced Community Medical Center. Centrally located to mountains and ocean. Ideal family living. Malpractice insurance provided. Teaching hospital with FP residency. For additional details send CV to: Robert Trautman, Merced Community Medical Center, P.O. Box 231, Merced, CA 95340; (209) 383-7225.

WANTED: Holistic physician nutritionally oriented to share office on part-time basis. Virginia Flanagan, MD, 13320 Riverside Dr., #112, Sherman Oaks, CA 91423. Phone (213) 995-4233.

FAMILY PRACTICE PHYSICIAN needed to work with a young Board Certified Family Practitioner in the beautiful Panhandle of North Idaho. Excellent specialty backup is available. Corporate benefits include a generous pension plan, excellent vacation and CME opportunities and a competitive salary. Applicant must like hard work and be willing to do obstetrics. Write Box 6188 Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

RADIOLOGIST—Practice position now available with established group of 3 radiologists in northern Utah. Primary responsibility will be for a 5 year old 50 bed HCA hospital in community of about 20,000. Ultrasound and limited angiography planned for department. Secondary rotation through a new 160 bed regional medical center with ultrasound, nuclear medicine, angiography and planned CT. For further details write or call James T. Shaw, MD, Logan Regional Hospital, Logan UT 84321. Telephone (801) 752-2050.

ASSOCIATES WANTED

A UNIQUE FAMILY PRACTICE opening for an associate interested in OB, minor surgery, surgery assistance, general medicine, pediatrics and emergency room care. Excellent financial arrangements. Private clinic building. Our own lab and x-ray and private parking for patients. Located in northwest 25 minutes from University of Washington Medical Center. All types of recreation. Good schools. Contact J. V. Curran, MD, Claremont Clinic; 5007 Claremont Way, Everett, WA 98203. Phone (206) 259-6603.

FAMILY PHYSICIAN or other primary care: To associate with long-established board certified FP. Recent ultra-modern medical office in high income area of Orange County. Major hospital close by. Community college and Calif. State Univ. in area, teaching—UCI. Write Box 6155, Western Journal of Medicine, 731 Merket St., San Francisco, CA 94103.

SITUATIONS WANTED

INTERNIST: Graduating medical resident, will take board in 9/81, seeks salaried position in internal medicine office or medical clinic in Bay Area. Box 6193, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

NEPHROLOGIST/INTERNIST board certified; 31; seeks practice or academic position in San Francisco after July, 1981. Experience in dialysis, transplantation, consults, clinical research. R. Fox, MD, 2042 W. Magnolia Ave., San Antonio, TX 78201. Phone (512) 732-4504.

SITUATIONS WANTED

CARDIOLOGIST, 35, Bd. Cert. 4 yrs. post Cert. Exp. Excellent Training. Prefers full-time Hospital based cardiology position. Available July, 1981. Seeks to relocate from East Coast to California. Reply Box 6186, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

INFECTIOUS DISEASE-INTERNIST. University trained, 30, ABIM certified. ID Board eligible. Desires opportunity in Infectious Disease/Internal Medicine in or near San Diego. Available July 1981. N. Kollisch, MD, 33 Pond Ave., Brookline, MA 02146. Tel (617) 566-0875.

INTERNIST—30, ABIM certified, moving to San Diego July 1981. Seeks position in Internal Medicine. Reply Box 6167, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

RADIOLOGISTS: Plan your 1981 vacation early. Board Certified coverage for your practice. Licensed all western states. Reserve early for best selection of dates. For further information reply c/o Box 6159, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

HEMATOLOGIST-ONCOLOGIST needed for busy, aggressive practice of same in Northern California community, one and a half hours from San Francisco. Teaching available. Send CV to Box 6153, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PATHOLOGIST, 45, certified AP-CP, excellent references, seeks relocation to San Francisco-San Jose area for permanent full-time or part-time practice. Box 6110, The Western Journel of Medicine, 731 Market St., San Francisco, CA 94103.

NEUROLOGIST, 37 years, Board certified and Board eligible by ABQEEG, wishes to relocate practice in California, in an area serving a population of 50-75,000. Please contact K. N. Sewa, MD, 24, Long Meadow Road, Trumbull, CT 06611.

OPTICIAN: California Registered Optical Dispenser desires to relocate dispensary and finishing lab near 2 or more non-dispensing Ophthalmologists. Southern Calif. area preferred but not a necessity. Box 6190, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

UROLOGIST finishing University residency program in June 1981 seeks solo or group practice. Available August, 1981. Wm. F. Remington, MD, 60 Grove St., Haddonfield, NJ 08033.

ORTHOPEDIC SURGEON. 52 years old. Board certified. Interested in office orthopedics and/or evaluations of disabilities. Part or full time. Write Box 6191, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

EXPERIENCED GP. Many years solo practice. Sale of office requires new location. Seeking opportunity for busy practice with good hospital facilities and off time coverage. Will lease, purchase or associate. California only. Box 6192, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

32—UNIVERSITY TRAINED. Board eligible. Seek position in General Surgery/Colon and Rectal Surgery. Licensed PA. Desires opportunity in California. Available August 1981. Chih J. Shieh, MD, 6201 N. 10th St. #336, Philadelphia, PA 19141.

FAMILY PRACTITIONER board qualified. Licensed California, Oregon, Washington, Minnesota. Age 47. Interested in all opportunities, prefer group practice, ER work, Industrial medicine, metropolitan or rural practice. Full or part time. Contact Robert L. Stein, MD, 1215 First Ave., No. Sauk Rapids, MI 56379. Tel (612) 255-0467.

SITUATIONS WANTED

BOARD CERTIFIED NEPHROLOGIST currently in academic position, extensively experienced in all phases of dialysis, seeks private practice opportunity. Box 6194, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

GENERAL PRACTITIONER—22 years practice in El Cajon, California. Retiring. Telephone 440-2202, 442-0887, 442-7797 all (714) area code.

TECHNICAL WRITER

TECHNICAL WRITER—Physician with medical and educational experience and technical writing training available for technical writing and editing. Clare Harper, MD, 120 Via Lerida, Greenbrae, CA 94904. (415) 461-4700.

LEGAL COUNSEL
SAMUEL SPITAL, ESQ.
1200 Third Avenue, Suite 1200
San Diego, CA 92101, (714) 231-4848
Former DEPUTY ATTORNEY GENERAL representing the Board of Medical Quality Assurance and Dept. of Health. Now specializing in B.M.Q.A. and defense malpractice matters throughout California.

LOCUM TENENS WANTED

LOCUM TENENS: Prestigious Sports Medicine/Preventive Medicine Center needs a board certified internist experienced in Stress Testing and giving complete physicals for one month, anytime early 1981. Write Box 6182, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

LOCUM TENENS: Nephrologist wanted for month of August 1981 to cover Out-patient Dialysis Unit and share call with two other Internists practicing in Vallejo. Adequate salary and home available, possible future association. Contact P. Philbin, MD, 123 Hospital Drive, Vallejo, CA. (707) 554-1170.

LOCUM TENENS WORK WANTED

EXPERIENCED BOARD CERTIFIED OB/GYN available for locum tenens work Northern California, preferably Bay Area. Spanish second language. Available end March. (408) 258-7056.

MEDICAL EQUIPMENT FOR SALE

X-RAY MACHINE—Picker 100ma portable, developing tanks, cassettes, everything needed for office x-ray, $4,000. P.O. Box AA, Idyllwild, CA 92349.

OFFICE EQUIPMENT, complete inventory from Family Practice office. New and under 2 years old. From x-ray machine to surgical instruments —$17,000. Write for inventory. Allan Abbott, MD, P.O. Box AA, Idyllwild, CA 92349.

LAB AVAILABLE

COMPLETE OFFICE LAB used under three months, includes Chem-Tek, Lyte-Tek, RIA Phase Gamma counter, bacteriologic set-up Cell-Trak and more. Call A. Berman, MD, (213) 596-1667.

PRACTICES AVAILABLE

BUYING or SELLING any type Medical Practice contact California Professional Practices, 2555 Huntington Dr., Suite D, San Marino, CA 91008. (213) 796-9262 or Agent Mr. Reilly (805) 543-4782 or Cliff Rauch (714) 997-0853.

PRACTICE SALES, PLACEMENT—Orthopedics, OB/GYN, Dermatology, Internal, Family, Pediatrics, Ophthalomology, ENT, etc. Partnerships, Appraisals. Professional Practice Opportunities, 21 Altamount Dr., Orinda, CA. (415) 376-0762.

SAN DIEGO AREA—Established GP leaving practice after 22 years in El Cajon. 1,000 sq. ft. office centrally located Medical center in El Cajon. Call: (714) 453-3990 or (714) 442-7797.

1,000 SQUARE FEET finished to occupy 4 exams, laboratory, reception plus 1,000 available to develop. $7 sq. ft. plus utilities. Dentists other occupant. Five Mile Med Dental Bldg, Spokane, WA; Elaine K. Glover, MD, 1625 W. Francis, Spokane, WA 99208. (509) 327-1503, (509) 466-6428.

MEDICAL OFFICE, be part owner, need one doctor, can lease 1,200 square feet, positive cash flow, available 7/15/81. 5 miles east of Auburn, Meadow Vista. Inquire: Fred Hampton (916) 878-2967.

OFFICE SPACE TO LEASE OR RENT

MEDICAL SUITES—Four offices available in Hemet, California. Fast growing retirement city in Southern Calif. Lease office from 714 sq. ft. to 1,624 sq. ft. at 45 cents sq. ft. One office with operating x-ray dept. and automatic processor. Cost negotiable for monthly x-ray use or equipment purchase. Prime location, walk to hospital. Call 925-2666 owner 9-5 Mon-Fri. Howard G. Lieberman, MD, 850 E. Latham Ave., Suite H, Hemet, CA 92343.

PSL

PRACTICE SALES & LOCATIONS

PRACTICES FOR SALE

All specialities available. Request practice list.

NEW OFFICE SET-UPS

Locations for lease, lease w/equity, purchase.

APPRAISALS

Practice appraisal for buyouts, dissolutions, etc. Widely accepted as the most comprehensive and rational.

PRACTICE SALES & LOCATIONS, INC.
17942 Skypark Circle, Suite D
Irvine, CA 92714
(714) 641-9203

MEDICAL SPACE AVAILABLE

MEDICAL SPACE FOR LEASE—975 or 1,700 sq. ft. Blossum Hill area-So. San Jose. MAR-LO Investments, (408) 727-1979.

SANTA CRUZ—Picture yourself in the office of your dreams as you designed it. If you can we have a project you may be interested in. Medical office space for lease. Approximately 1,050 square feet available in early construction stage. Leasee may be in on final design decisions. Located near Dominican Hospital in developing professional region. Expect occupancy April 1981. Please call (408) 426-4655.

FLAGSTAFF MEDICAL BUILDING LEASE AND OWN

Located next to the Flagstaff Hospital and Medical Center on the corner of Forest and Beaver Streets. A Pharmacy, laboratory and radiology in the complex plus parking easily accessible to either your office or the hospital makes the Flagstaff Medical Building the desired choice for the largest number of practicing physicians in any medical building located in Northern Arizona. Your customized medical office suite (ranging from 800 to 2,000 sq. ft.) is now available at a most reasonable cost plus the existing partnership is now offering those tenants signing leases before May 15, 1981 the opportunity to purchase an ownership interest in the building. Please contact:

BRUCE O. UTTERBACH, CPM, FLAGSTAFF MEDICAL BUILDING, 1355 N. BEAVER, FLAGSTAFF, ARIZONA 86001. (602) 774-4416.

MEDICAL SPACE TO SHARE

PACIFIC PALISADES, CALIFORNIA. Board eligible or certified Internist, Family Practitioner, Surgeon or other specialist (adult/adolescent) to share suite in new professional building. Two exam rooms, private office. Share reception area. (213) 459-7506 eves. and weekends, 825-0519 days.

RENTAL (OFFICE): South Orange County, California. Sub specialized or gen. surgeon or GP to pro rata share 1,520 sq. ft. new modern, fully equipped medical suite, in large hosp. complex. Ideally loc. adj. all maj. hosp., recreation, countryside. Please call and send CV with photo to: Robert L. Epps, MD, 23961 Calle de la Magdalena, #300, Laguna Hills, CA 92653. Telephone (714) 770-6679.

Business-Free Medicine?

Want to practice medicine and enjoy more time off for yourself? **FHP**, one of Utah's most established HMO's, is currently seeking **Family Practitioners** who believe in predictable work hours and wish to practice quality health care without the usual business worries. If you would like a guaranteed income and an opportunity to practice within a stable and innovative medical organization, call or write today:
Ralph Brown (801) 355-1234

FHP FAMILY HEALTH PROGRAM
323 South 600 East, Salt Lake City, Utah 84102

THE WESTERN Journal of Medicine

CLASSIFIED RATES

$4.00 PER LINE

(Average six words per line)

FIVE LINE MINIMUM
BOX NUMBERS $2.00 EXTRA

• • •

DISPLAY CLASSIFIED

$40 PER COLUMN INCH

Three column page rate available on request

COLUMN WIDTH
1 column 2⅛″ • 2 columns 4½″ • 3 columns 7″
(Classified Advertising is payable in advance)
Please type or print advertising copy

DEADLINE
1st of Month before publication date

731 MARKET STREET
SAN FRANCISCO, CA 94103 • (415) 777-2000

for your patients with moderate depression and anxiety

RELIEF WITHOUT A

The choice without a phenothiazine

☐ provides the specifically effective antianxiety action of Librium® (chlordiazepoxide HCl/Roche), with its outstanding safety record, together with the well established antidepressant effect of amitriptyline.

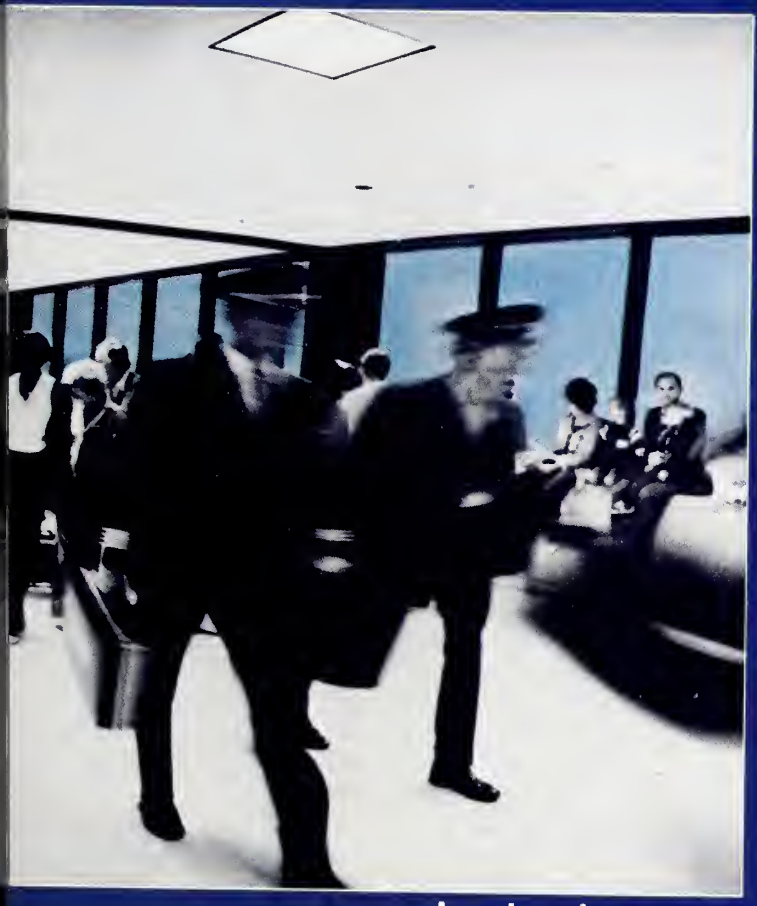
☐ symptoms likely to respond in the first week of treatment include insomnia, anorexia, psychic and somatic anxiety, agitation and feelings of guilt or worthlessness.

A better choice because

☐ minimizes risk of tardive dyskinesia and other extrapyramidal side effects. The causal relationship between the phenothiazines and extrapyramidal side effects, including tardive dyskinesia, is well established. In contrast, the reported incidence of these adverse reactions with Limbitrol or either of its components is rare.

ROCHE®

PHENOTHIAZINE



What better reason to switch from a phenothiazine combination and start prescribing

Limbitrol® IV

Tablets 5-12.5 each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)

Tablets 10-25 each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt)

Please see following page for summary of product information.

LIMBITROL® TABLETS Tranquilizer—Antidepressant

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Relief of moderate to severe depression associated with moderate to severe anxiety

Contraindications: Known hypersensitivity to benzodiazepines or tricyclic antidepressants. Do not use with monoamine oxidase (MAO) inhibitors or within 14 days following discontinuation of MAO inhibitors since hyperpyretic crises, severe convulsions and deaths have occurred with concomitant use; then initiate cautiously, gradually increasing dosage until optimal response is achieved. Contraindicated during acute recovery phase following myocardial infarction.

Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients. (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

***Usage in Pregnancy*: Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage; withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline; symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).

Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. Concomitant use with other psychotropic drugs has not been evaluated sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy.

Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.

Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.

The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs:

Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.

Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido.

Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.

Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.

Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.

Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.

Endocrine: Testicular swelling and gynecomastia in the male; breast enlargement, galactorrhea and minor menstrual irregularities in the female and elevation and lowering of blood sugar levels.

Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single h.s. dose may suffice for some patients. Lower dosages are recommended for the elderly.

Limbitrol 10-25, initial dosage of three to four tablets daily in divided doses, increased up to six tablets or decreased to two tablets daily as required. Limbitrol 5-12.5, initial dosage of three to four tablets daily in divided doses, for patients who do not tolerate higher doses.

How Supplied: White, film-coated tablets, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt) and blue, film-coated tablets, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt) - bottles of 100 and 500, Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10, Prescription Paks of 50.

ROCHE®

ROCHE PRODUCTS INC
Manati, Puerto Rico 00701

Your guide to patient management... when you decide medication is needed

How to initiate and maintain therapy

Select dosage strength appropriate for each patient

- Limbitrol 5-12.5 is recommended to minimize drowsiness and for elderly patients.
- Limbitrol 10-25 may be indicated for patients who tolerate medication without undue side effects.

Specify daily dosage based on symptom severity

- An initial dosage of three tablets is recommended.
- Dosage may be increased to six tablets or decreased to two tablets daily as necessary.
- Once a satisfactory response is obtained, patients should be continued on the smallest dose required to maintain the desired effect.

Utilize dosage options to best accommodate individual patient needs

- T.I.D. or Q.I.D., familiar regimens most suited for patients who tolerate medication without undue drowsiness.
- Two tablets one hour before bedtime and one tablet midday may minimize daytime drowsiness and help relieve a common target symptom – insomnia.
- Entire dosage h.s. to take maximum advantage of the sedative effect.

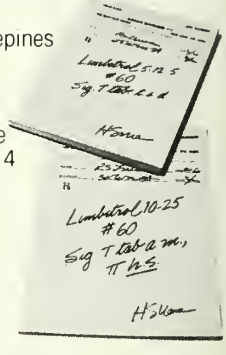
How to make each patient an informed patient

1. Discuss with patients the probability that they will experience drowsiness, especially during the first week.
2. Reassure your patients that drowsiness is one indication that the medication is working and that it may help alleviate their insomnia.
3. Encourage patients to report if drowsiness becomes troublesome so that, if necessary, dosage schedule can be adjusted.
4. Caution patients about the combined effects with alcohol or other CNS depressants. Let them know that the additive effects may produce a harmful level of sedation and CNS depression.
5. Caution patients about activities requiring complete mental alertness, such as operating machinery or driving a car.
6. Warn pregnant patients and patients of childbearing age that the safety of Limbitrol in pregnancy has not yet been established.

Please see complete product disclosure for other pertinent information.

Limbitrol should not be used under the following circumstances:

1. Hypersensitivity to benzodiazepines or tricyclic antidepressants.
2. Concomitantly with an MAO inhibitor. To replace an MAO inhibitor with Limbitrol, discontinue MAO inhibitor for a minimum of 14 days before cautiously initiating Limbitrol therapy.
3. During the acute recovery phase following myocardial infarction.



In moderate depression and anxiety

Limbitrol® IV

Relief without a phenothiazine

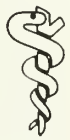
CHECKING INTO MEDICAL MALPRACTICE INSURANCE?

CHECK OUT SOME FACTS	NORCAL MUTUAL Insurance Company	Physicians & Surgeons Insurance Exchange	The Doctor's Company
WHICH COMPANY IS DOCTOR OWNED ?	☑	☑	☑
WHICH DOES NOT REQUIRE SUBORDINATED LOAN/SURPLUS CONTRIBUTIONS ?	☑	☑	☐
WHICH IS RETURNING SUBORDINATED LOAN/SURPLUS CONTRIBUTIONS ?	☑	☐	☐
WHICH IS ENDORSED AND SPONSORED BY 24 LOCAL MEDICAL SOCIETIES ?	☑	☐	☐
WHICH HAS THE HIGHEST TOTAL ASSETS AND RESERVES ?	☑	☐	☐
WHICH HAS A SYSTEM OF PREMIUM CREDITS TOWARD RETIREMENT ? *	☑	☐	☐

NORCAL offers coverage to northern California physicians.

If you want more facts, call us toll-free at (800) 652-1051.

Or, call your Medical Society. They've been checking into medical malpractice insurance for years.



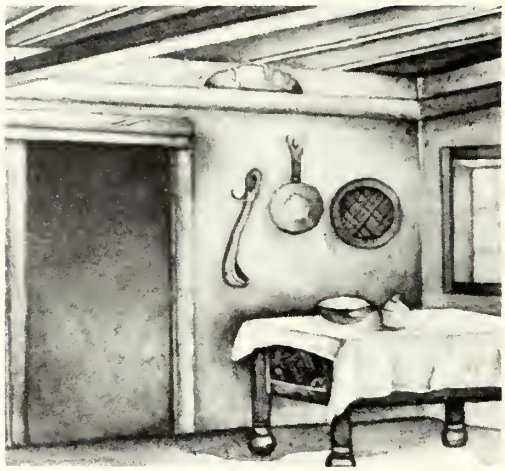
NORCAL MUTUAL INSURANCE COMPANY
333 Market Street, San Francisco, CA 94105
(415) 777-4200 or (800) 652-1051 (toll-free)

---

*NORCAL MUTUAL is the only company offering run-off premium credits to retiring physicians insured with the Company less than 5 years.

Yesterday's Folk Remedy:

A rye loaf in the rafters.



Early in this century in Central Europe, almost every farm family kept a loaf of moldy rye bread on one of the kitchen beams. When any family member was cut or bruised, it was an old custom to cut a thin slice from the outside of the loaf, mix it into a paste with water, and apply it to the wound with a bandage. It was believed that no infection would then result from the cut.[1]

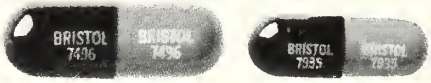
Today's Tradition: Tegopen® (cloxacillin sodium)

for the treatment* of known or suspected staphylococcal infections such as:

- Acute sinusitis
- Furunculosis and carbuncles
- Impetigo
- Secondarily infected dermatitis
- Cellulitis
- Abscesses
- Infected sebaceous cysts

In serious, deep-seated staph infections, 500 mg q.i.d. dosage is recommended.†

- Tegopen has been reported active against 96% of *Staphylococcus aureus*.[2]
- 80% of *S aureus* has been reported resistant to amoxicillin and ampicillin.‡[2]
- 88% of *S aureus* has been reported resistant to penicillins G and V.‡[2]
- Staph resistance to erythromycin may develop during a course of therapy.[3]



Available as 500-mg and 250-mg capsules and Oral Solution 125 mg/5 ml.

Tegopen® (cloxacillin sodium) Today's Penicillin for Today's Physician

1 Florey HW, Chain E, Heatley NG, et al: *Antibiotics*. London, Oxford University Press, 1949, p 2.

2 Bac-Data Bacteriologic Report, Professional Market Research, 1978-1979. The clinical significance of *in vitro* data is unknown

3. Erythromycin prescribing information (in *Physicians' Desk Reference*, ed 34. Oradell, NJ, Medical Economics Co, 1980) states that staph resistance may develop during treatment.

See brief summary of prescribing information on an adjoining page.

Copyright © 1981, Bristol Laboratories

*Note: The choice of Tegopen should take into consideration the fact that it has been shown to be effective only in the treatment of infections caused by pneumococci, Group A beta-hemolytic streptococci, and penicillin G-resistant and penicillin G-sensitive staphylococci. If the bacteriology report later indicates that the infection is due to an organism other than a penicillin G-resistant staphylococcus sensitive to cloxacillin sodium, the physician is advised to continue therapy with a drug other than cloxacillin sodium or any other penicillinase-resistant semisynthetic penicillin.

†In serious, life-threatening infections, oral preparations of the penicillinase-resistant penicillins should not be relied on for initial therapy.

‡Not all isolates may have been tested using both discs

Tegopen®
(cloxacillin sodium)
Capsules and Oral Solution

Brief Summary of Prescribing Information
For complete information, consult Official Package Circular
(12) 9/11/75

INDICATIONS:
Although the principal indication for cloxacillin sodium is in the treatment of infections due to penicillinase-producing staphylococci, it may be used to initiate therapy in such patients in whom a staphylococcal infection is suspected. (See Important Note below.)

Bacteriologic studies to determine the causative organisms and their sensitivity to cloxacillin sodium should be performed.

IMPORTANT NOTE:
When it is judged necessary that treatment be initiated before definitive culture and sensitivity results are known, the choice of cloxacillin sodium should take into consideration the fact that it has been shown to be effective only in the treatment of infections caused by pneumococci, Group A beta-hemolytic streptococci, and penicillin G-resistant and penicillin G-sensitive staphylococci. If the bacteriology report later indicates the infection is due to an organism other than a penicillin G-resistant staphylococcus sensitive to cloxacillin sodium, the physician is advised to continue therapy with a drug other than cloxacillin sodium or any other penicillinase-resistant semi-synthetic penicillin.

Recent studies have reported that the percentage of staphylococcal isolates resistant to penicillin G outside the hospital is increasing, approximating the high percentage of resistant staphylococcal isolates found in the hospital. For this reason, it is recommended that a penicillinase-resistant penicillin be used as initial therapy for any suspected staphylococcal infection until culture and sensitivity results are known.

Cloxacillin sodium is a compound that acts through a mechanism similar to that of methicillin against penicillin G-resistant staphylococci. Strains of staphylococci resistant to methicillin have existed in nature and it is known that the number of these strains reported has been increasing. Such strains of staphylococci have been capable of producing serious disease, in some instances resulting in fatality. Because of this, there is concern that widespread use of the penicillinase-resistant penicillins may result in the appearance of an increasing number of staphylococcal strains which are resistant to these penicillins.

Methicillin-resistant strains are almost always resistant to all other penicillinase-resistant penicillins (cross-resistance with cephalosporin derivatives also occurs frequently). Resistance to any penicillinase-resistant penicillin should be interpreted as evidence of clinical resistance to all, in spite of the fact that minor variations in *in vitro* sensitivity may be encountered when more than one penicillinase-resistant penicillin is tested against the same strain of staphylococcus.

CONTRAINDICATIONS:
A history of a previous hypersensitivity reaction to any of the penicillins is a contraindication.

WARNING:
Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents, e.g., pressor amines, antihistamines, and corticosteroids.

Safety for use in pregnancy has not been established.

PRECAUTIONS:
The possibility of the occurrence of superinfections with mycotic organisms or other pathogens should be kept in mind when using this compound, as with other antibiotics. If superinfection occurs during therapy, appropriate measures should be taken.

As with any potent drug, periodic assessment of organ system function, including renal, hepatic, and hematopoietic, should be made during long-term therapy.

ADVERSE REACTIONS:
Gastrointestinal disturbances, such as nausea, epigastric discomfort, flatulence, and loose stools, have been noted by some patients. Mildly elevated SGOT levels (less than 100 units) have been reported in a few patients for whom pretherapeutic determinations were not made. Skin rashes and allergic symptoms, including wheezing and sneezing, have occasionally been encountered. Eosinophilia, with or without overt allergic manifestations, has been noted in some patients during therapy.

USUAL DOSAGE:
Adults: 250 mg. q 6h.

Children: 50 mg./Kg./day in equally divided doses q 6h. Children weighing more than 20 Kg. should be given the adult dose. Administer on empty stomach for maximum absorption.

N.B. INFECTIONS CAUSED BY GROUP A BETA-HEMOLYTIC STREPTOCOCCI SHOULD BE TREATED FOR AT LEAST 10 DAYS TO HELP PREVENT THE OCCURRENCE OF ACUTE RHEUMATIC FEVER OR ACUTE GLOMERULONEPHRITIS.

SUPPLIED:
Capsules—250 mg. in bottles of 100, 500 mg. in bottles of 100.
Oral Solution—125 mg./5 ml. in 100 ml. and 200 ml. bottles.

BRISTOL®
Bristol Laboratories
Division of Bristol-Myers Company
Syracuse, New York 13201

Physicians—Stress & Coping

Weekend Workshops for Physicians and Spouses

During this weekend, physicians and spouses, together with faculty, will examine sources of stress, stress reduction strategies and concerns unique to physicians and their family members.

- ☐ **April 24-26**, Stanford Sierra Lodge, South Lake Tahoe
- ☐ **May 22-24**, Carmel Valley Inn
- ☐ **May 29-31**, Stanford Sierra Lodge, South Lake Tahoe
- ☐ **June 12-14**, Aliso Creek Inn, South Laguna
- ☐ **June 19-21**, The Inn, Rancho Santa Fe

For each weekend, there is a registration fee and a separate fee for room and board. Registration is $165 per couple or $100 per person.

For information and to register, contact California Medical Association, Committee on the Well-Being of Physicians, 731 Market Street, San Francisco, CA 94103. Call (415) 777-2000, Ext. 138

1981 Postgraduate Seminars

FACULTY:
Conducted by nationally-renowned cardiologists and authorities with special expertise in these areas.

CREDIT:
- 13 hours Category I A.M.A.
- 13 Prescribed hours A.A.F.P.
- 13 hours Category I A.C.E.P.
- 13 hours A.N.A.

LOCATIONS:
2 day and 2 ½ day weekend seminars held in over thirty metropolitan and resort locations.

Arrhythmias & Cardiac Ischemia: Diagnosis & Management

May 8-10, 1981
Las Vegas, Nevada

June 26-28, 1981
Orlando, Florida

July 17-19, 1981
Cape Cod, MA

August 14-16, 1981
Montreal, Canada

September 11-12, 1981
Chicago, Illinois

September 18-20, 1981
Las Vegas, Nevada

October 23-24, 1981
Atlanta, Georgia

Clinical Management of Coronary Disease and Exercise Testing

May 1-2, 1981
San Francisco, CA

June 12-14, 1981
Las Vegas, Nevada

June 19-21, 1981
Williamsburg, VA

June 26-28, 1981
Toronto, Canada

July 17-19, 1981
Lake Geneva, WI

July 24-25, 1981
Nashville, Tennessee

August 14-16, 1981
Hilton Head, SC

ECG Interpretation & Arrhythmia Management

May 8-10, 1981
St. Petersburg, FL

June 26-28, 1981
Anaheim, California

July 31-Aug. 2, 1981
Bellaire, Michigan

August 7-8, 1981
Monterey, California

August 28-30, 1981
Orlando, Florida

October 2-3, 1981
Cincinnati, Ohio

October 30-31, 1981
Chicago, Illinois

Cardiac Rehabilitation

May 1-2, 1981
Chicago, Illinois

July 24-25, 1981
Orlando, Florida

August 21-22, 1981
Anaheim, California

October 16-17, 1981
Philadelphia, PA

December 4-5, 1981
Denver, Colorado

IMEC

■ For information on these and other courses, contact Director of CME, Dept. 7, International Medical Education Corporation 64 Inverness Drive East, Englewood, Colorado 80112/Tel. (303) 773-1144 or **Toll Free (800) 525-8646**

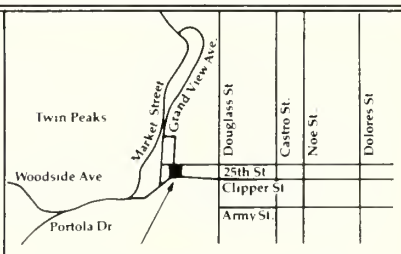
Nob Hill is beneath us.

Grand View Terrace puts you at the top in San Francisco. These contemporary town house condominiums offer a standard of luxury befitting their high position.

First, they're wonderfully spacious and airy, with bay windows that command a magnificent panoramic view of the entire Bay Area. And each home has over-sized rooms with 9 foot ceilings, extra wide hallways, wood burning fireplaces, skylights, individual dressing rooms, large closets, redwood decks and a one or two car garage. Some have garden atriums.

Come see it all. The grand view, luxurious interiors and the spacious quality that comes from living near the top of Twin Peaks in San Francisco.

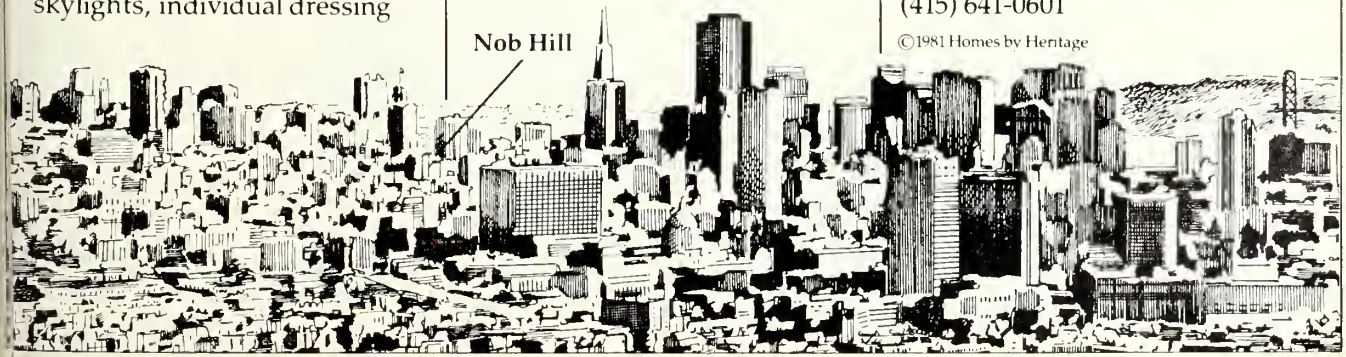
Prices range from $265,000 to $325,000. Model home open daily from 1 to 5 pm, 7 days a week, 760 Clipper Street, just below Grand View. For inquiries and appointments, call Homes by Heritage (415) 641-0601.



Grand View Terrace

Clipper and Grand View Streets
San Francisco, CA 94114
(415) 641-0601

©1981 Homes by Heritage



Northridge Hospital Foundation
presents

ONCOLOGY UPDATE 1981

saturday
april 25, 1981
7:30 am–5:30 pm

CENTURY PLAZA HOTEL
Los Angeles

distinguished faculty and topics

Martin Cline, M.D., U.C.L.A.
"Bone Marrow Transplantation"

Sydney E. Salmon, M.D., University of Arizona
"Adjuvant Chemotherapy of Cancer"

Leonard R. Prosnitz, M.D.,
"Hodgkin's Disease—State of the Art, 1981"

F. Kristian Storm, M.D., U.C.L.A
"Hyperthermia Cancer Therapy"

Robert B. Livingston, M.D.,
Cleveland Clinic Foundation
"Current Management of Localized and Disseminated Breast Cancer"

Jordan Gutterman, M.D.,
"Interferon—An Overview"

Fees: $125 Physicians, $50 Nurses, $25 students

registration form

specialty _____

name _____ ph _____

address _____

affiliation _____

☐ physician ☐ reg. nurse, R/N lic

☐ student/paramedical ☐ other

for more information:
Dept. of Medical Education
Northridge Hospital Foundation
18300 Roscoe Blvd.
Northridge, CA 91328
(213) 885-5311

Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

Ativan® IV for Anxiety (lorazepam)

Dosage: **Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; Insomnia due to anxiety or transient situational stress, 2-4mg h.s.**

How Supplied: **0.5, 1.0 and 2.0mg tablets.**

Copyright © 1981, Wyeth Laboratories
All rights reserved

Wyeth Laboratories
Philadelphia, PA 19101

Four practical reasons to prescribe Ativan® (lorazepam) Ⓒ Ⓥ for Anxiety*

1 No interaction with more than 300 drugs+

In clinical studies, Ativan was given concomitantly with hundreds of medications, including gastrointestinal and cardiovascular, with no reported interactions. Whereas the interaction of diazepam and cimetidine has been shown to cause increased sedation in patients taking both drugs, the clearance of Ativan is not delayed by Tagamet.‡

2 Lets most patients stay active

Long-acting benzodiazepines have long-acting metabolites with activity which can produce excessive accumulation that may lead to unwanted sedation. Ativan® has no active metabolites, reaches steady state in 2 to 3 days and usually does not cause oversedation. Also, the shorter half-life of Ativan is consistent with b.i.d. dosage, so drug hangover is seldom a problem the next morning.

3 Not appreciably affected by aging

Unlike the long-acting benzodiazepines—diazepam Ⓒ Ⓥ, chlordiazepoxide Ⓒ Ⓥ, clorazepate Ⓒ Ⓥ and prazepam Ⓒ Ⓥ—the metabolism and clearance of Ativan are not appreciably affected by the aging process.

4 Not significantly affected by liver dysfunction

Ativan® is metabolized in one simple step to an inactive glucuronide; its absorption and excretion are not significantly altered by cirrhosis or hepatitis. By contrast, the metabolism of diazepam and chlordiazepoxide has been reported to be significantly altered in patients with liver dysfunction.

See important information on following page.

Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

All benzodiazepines, however, produce additive effects when given with CNS depressants, such as barbiturates or alcohol.

Tagamet (cimetidine) is a registered trademark of Smith Kline & French Laboratories, Division of SmithKline Corporation.

Copyright © 1981, Wyeth Laboratories. All rights reserved

Wyeth Laboratories
Philadelphia, PA 19101
™

"My doctor restricts my diet, but not my taste."

"That's why I use Mocha Mix®, the fresh, non-dairy creamer."

Steve Allen
Noted composer, author and TV personality.

"I'm allergic to milk, but I hate black coffee. My wife Jayne and I discovered Mocha Mix, and I'm back to smiling in the morning. You see, Mocha Mix is 100% milk-free. It has no animal fat, cholesterol, or coconut oil. It's the lowest in saturated fats of all creamers. And, it's perfect for restricted diets. Mocha Mix is so great tasting, we both use it on cereal, fresh fruit—almost anything. Jayne loves it in most any recipe calling for milk or cream."

Mocha Mix has the highest ratio of polyunsaturated to saturated fat of any creamer, exceeding the accepted standard 2 to 1 ratio.

Mocha Mix can be the delicious answer for your patients who are allergic to milk or have a lactose intolerance or for patients who require restricted diets.

"How's that for a 'meeting of the minds,' doctor?"

FREE! AN INFORMATIVE RECIPE BOOKLET, MENU PLANNER AND MONEY-SAVING COUPONS ARE YOURS FREE—FOR THE ASKING!

Just drop us a note and we'll be happy to send you a supply of this recipe booklet containing low-fat, low-cholesterol recipes and menu ideas as well as a supply of money-saving coupons your patients can redeem at their grocers. Hospital service may be supplied upon request.

WRITE TO:
MOCHA MIX, DEPT. M
PRESTO FOOD PRODUCTS, INC.
P.O. BOX 21908
Los Angeles, California 90011

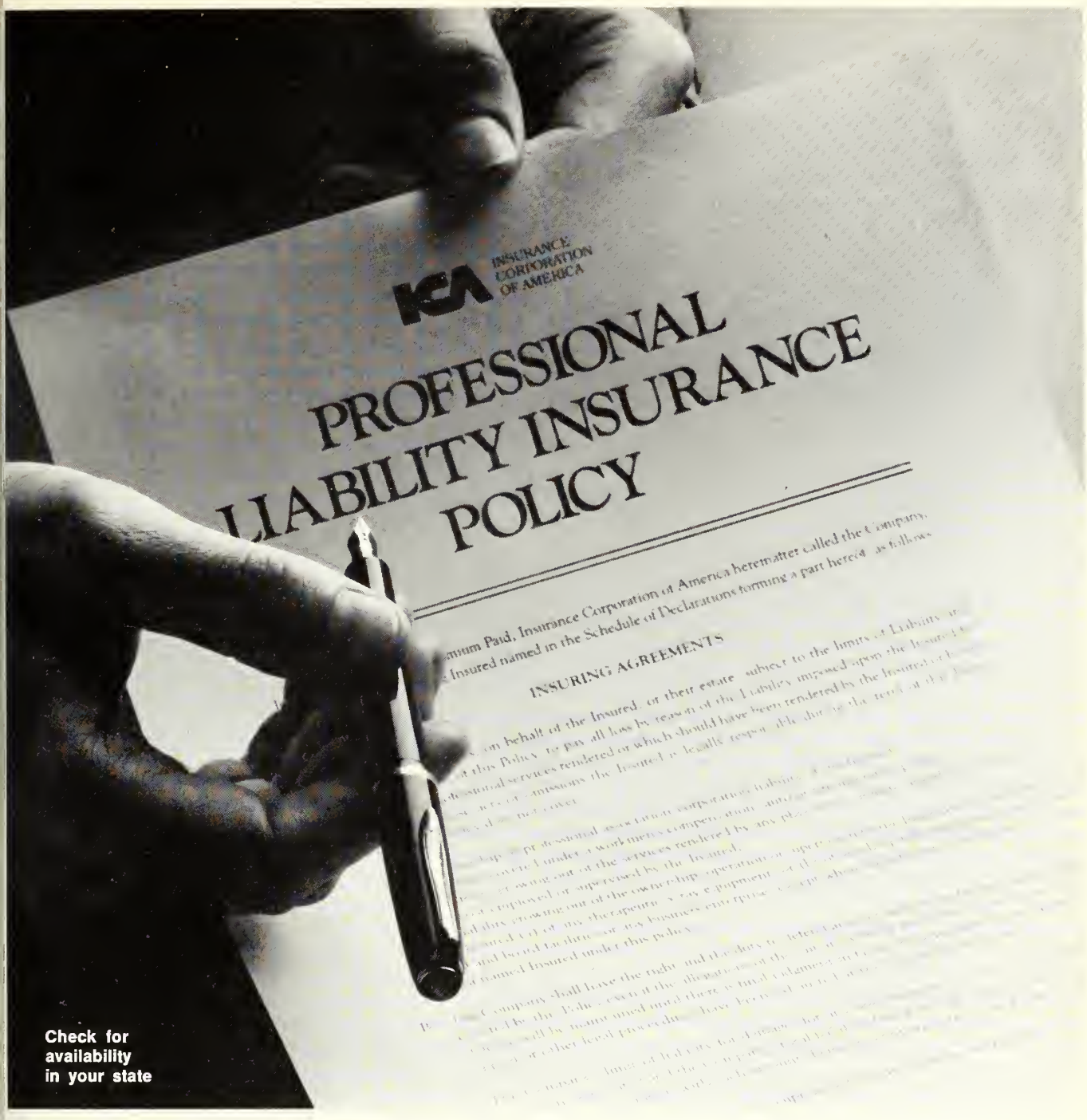
NUTRITIONAL INFORMATION

Portion Size 1 Fluid Ounce (2 Tbs.)	
Servings per Container	16
Calories	40
Protein	0 grams
Carbohydrate	3 grams
Fat	3 grams
Percent of Calories from Fat	73%
Polyunsaturated Fat	1 gram
Saturated Fat	0 grams
Cholesterol (△) (0 mg./100g)	0 mg
Sodium	21 mg
Calcium	2 mg
Potassium	37 mg.
Phosphorus	15 mg.

Percentage of U.S. Recommended Daily Allowance (U.S. RDA)*
*Contains less than 2% of the U.S. RDA of Protein, Vitamin A, Vitamin C, Thiamin, Calcium, Riboflavin, Niacin, Iron.
△ Information on fat and cholesterol content is provided for individuals who, on the advice of a physician are modifying their total dietary intake of fat and cholesterol.

NOTE: In addition to the pint and quart size found in the dairy case at most grocery stores, Mocha Mix is also available in ½ gal., as well as 4 oz. and ½ oz. portion packs for hospitals and institutions.

Mocha Mix is available **only** in California, Arizona, Nevada, Oregon, Washington and Denver, CO



PUT A CONTRACT OUT ON FRIVOLOUS CLAIMS.

Frivolous claims can be a nightmare. Especially if your malpractice insurance company doesn't stand by you. And unfortunately, all too many don't.

For instance, most malpractice insurance policies give you no say in whether to fight or settle a claim. And if you do have a say, you can be hit with a costly penalty for going to court. Another thing. Many companies don't pay all legal expenses. And most companies seldom use lawyers to process cases. Claims are often handled only by claims adjusters.

It's a different story at Insurance Corporation of America. ICA is a doctor and attorney owned company working for doctors. So we know the strong coverage and knowledgeable service physicians need from their liability insurance. And since we specialize in this one field, we can offer a superior policy for a realistic premium. Premiums based on actual costs in your state.

So select the policy with the protection you need. Put a contract out on frivolous claims. For more information contact: Insurance Corporation of America, ICA Building, 2205 Montrose, Houston, Texas 77006. 713-526-4863. Outside Texas Phone 1-800-231-2615

ICA INSURANCE CORPORATION OF AMERICA

MALPRACTICE INSURANCE IS BETTER TODAY. BECAUSE OF ICA.

CALIFORNIA MEDICAL ASSOCIATION

1981 Postgraduate Institutes

SAN JOAQUIN VALLEY COUNTIES

The Ahwahnee, Yosemite
April 23-25

- Recognition & Treatment of Coronary Artery Spasm
- Recognition of Anxiety & Stress Disorders
- New Viruses
- Adolescent Gynecology
- Basic Neurological Examination
- Rational Diagnosis & Treatment of Emotional Problems in Geriatric Patients
- New Concepts in Diagnosis & Treatment of Hypertension

Faculty from UC San Diego Medical School

HUMAN SEXUALITY

Claremont, Berkeley
June 11-13

Choice of three one-hour workshops

- Sexual Counseling in Chronic & Acute Illness
- Children & Adolescent Sexuality
- Sexual Variation
- Middle Adults & Older Patients
- Office Treatment of Specific Sexual Problems

Additional topics to be offered

Faculty provided by five UC Medical Schools

WEST COAST COUNTIES

Doubletree Inn, Monterey
October 22-24

Update for Primary Care Physicians

Faculty from UCSF

✧ ✧ ✧

These programs are accredited for category one credit

✧ ✧ ✧

Hotel space is limited — early reservations are suggested

Complete program and hotel information will be sent by return mail.
Use the tear off sheet below or call CMA (415) 777-2000, extension 143.

1981 CMA POSTGRADUATE INSTITUTES

I plan to attend the following Postgraduate Institute(s):

☐ **San Joaquin Valley Counties**
April 23-25, Yosemite

☐ **Human Sexuality**
June 11-13, Berkeley

☐ **West Coast Counties**
October 22-24, Monterey

FEE: $75.00 for **each** institute
($125.00 for non-CMA Members)

Please make check payable to
California Medical Association

Name _____ Specialty _____

Address _____

City _____ Zip _____

County _____

Number of years out of Medical School _____

Mail to: CMA, Continuing Medical Education, 731 Market Street, San Francisco, CA 94103
Attn: Charlotte Newhart. A program and hotel reservation form will be sent to you.

(Continued from Page 19)

September 25-26—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Holiday Inn, San Francisco. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112, (800) 525-8646.

October 3—**4th Annual Heart Symposium.** Northridge Hospital at Century Plaza Hotel, Los Angeles. Saturday. Contact: Dept. of Med. Ed., Northridge Hospital, 18300 Roscoe Blvd., Northridge 91328. (213) 885-8500.

October 16-17—**Advances in Internal Medicine.** So. Calif. Permanente Medical Group at Century Plaza Hotel, Los Angeles. Friday-Saturday. Contact: Shirley Gach, Education and Research, SCPMG, 4747 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

October 16-18—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Sahara Hotel, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

October 18-22—**Pacific Dermatologic Association—Annual Meeting.** Reno. Monday-Thursday. Contact: Florence Beardsley, Exec. Sec., PDA, 180 Mark Twain Ave., Reno 89509. (702) 323-2461.

OBSTETRICS AND GYNECOLOGY

April 25-30—**American College of Obstetricians and Gynecologists.** Convention Center, Las Vegas. Saturday-Thursday. Contact: W. H. McDannel, Convention Mgr., ACOG, 1 E. Wacker Dr., Suite 2700, Chicago 60601. (312) 222-1600.

May 11-13—**Recent Advances in Obstetrics and Gynecology.** UCSD at Vacation Village, San Diego. Monday-Wednesday. 18 hrs.

June 10—**Carcinomas of the Uterus and Ovaries.** See Cancer, June 10.

August 8-15—**Reproductive Endocrinology, Infertility and Contraception.** See Of Interest To All, August 8-15.

August 29-September 5—**Concepts in Infertility.** See Of Interest To All, August 29-September 5.

PEDIATRICS

May 1-2—**The Physician and the Handicapped Child: New Directions.** American Academy of Pediatrics and State Dept. of Education at Sacramento. Friday-Saturday. Contact: Peter Miller, MD, Marin Co. Civic Ctr., Rm. 280, Dept. of Health and Human Services, San Rafael 94903. (415) 499-6877.

May 4-8—**11th Annual Review of Pediatrics.** USC. Monday-Friday. $300.

May 6-8—**Care of the Sick Newborn—6th Annual Symposium.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. Contact: Prog. Coordinator, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

May 13—**Genetic Counseling.** LLU. Wednesday. 4 hrs. $30.

May 13—**Pediatric Symposium.** American Heart Assn.-Greater Los Angeles Affiliate and Los Angeles Pediatric Soc. at USC. Wednesday. 6 hrs. Contact: LaVerna M. Titus. AHA-GLAA, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

May 14-16—**Advances in Pediatrics.** UCSF at Mark Hopkins Hotel, San Francisco. Thursday-Saturday.

May 15-16—**23rd Annual Pediatric Symposium.** So. Calif. Permanente Medical Group at Hyatt Regency, Los Angeles. Friday-Saturday. Contact: Shirley Gach, SCPMG, Education and Research Dept., 4747 Sunset Blvd., 4th Floor, Los Angeles 90027. (213) 667-4241.

May 20-25—**Pediatrics for the Primary Care Physician and All That Jazz.** UCD at Sacramento. Wednesday-Monday.

May 30—**The Child With Facial Deformity: A Progress Report.** See Surgery, May 30.

October 2-3—**Pediatric Topics.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday. 10 hrs.

October 18—**The Hearing Impaired: Identification, Counseling and Rehabilitation.** Peninsula Hospital and San Mateo Co. Office of Education at Peninsula Hospital, Burlingame. Sunday. Contact: Les Demme, Peninsula Hosp. and Med. Ctr., 1783 El Camino Real, Burlingame 94040. (415) 697-4061.

PSYCHIATRY

June 3-4—**Brief Therapy.** Dept. of Health, Health Training Center/North, at Chico. Wednesday-Thursday. 12 hrs. Contact: Health Training Center, 5850 Shellmound St., Suite 390, Emeryville 94608. (415) 464-0685.

June 3-4—**Communicating With Schizophrenics.** Dept. of Health, Health Training Center/North, Emeryville. Wednesday-Thursday. 12 hrs. Contact: Health Training Ctr., 5850 Shellmound St., Suite 390, Emeryville 94608. (415) 464-0685.

June 24-25—**Crisis Intervention.** Dept. of Health, Health Training Center/North, Emeryville. Wednesday-Thursday. 12 hrs. Contact: Health Training Ctr., 5850 Shellmound St., Suite 390, Emeryville 94608. (415) 464-0685.

June 28-30—**Family Problems, Aging and Sexuality.** See Of Interest To All, June 28-30.

July 8-10—**Update in Psychiatry: Psychopharmacology.** UCSD at Hanalei Hotel, San Diego. Wednesday-Friday.

July 31-August 1—**Innovations: New Trends in Family Therapy, Brief Therapy and Family Medicine.** Mental Research Institute at Sheraton-Palace, San Francisco. Friday-Saturday. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

August 15-21—**Neuropsychiatric Issues in the Law, Education and Medicine: Hyperactivity and Dyscontrol Syndrome.** So. Calif. Neuropsychiatric Institute and Hawaii Psychiatric Society at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 15 hrs. Contact: Gail Waldron, MD, 6794 La Jolla Blvd., La Jolla 92037. (714) 454-2102.

RADIOLOGY AND PATHOLOGY

April 25—**Cytodiagnosis in Medical Practice.** UCLA. Saturday. 6 hrs. $125.

May 2-9—**Liver Pathology Workshop.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

May 8-9—**Gastrointestinal Imaging in Perspective.** See Medicine, May 8-9.

May 24-29—**The Pathologist as a Clinical Consultant.** UCD at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

June 1-4—**Diagnostic Cytology of the Female Genital Tract.** American Society of Clinical Pathologists at San Francisco. Monday-Thursday. 22½ hrs. $450, members; $550, nonmembers. Contact: Marian Macdonald, Admin. Asst., ASCP, 2100 W. Harrison St., Chicago 60612. (312) 738-1336.

June 3-5—**Radiology in the Emergency Room.** UCSF at Golden Gateway Holiday Inn, San Francisco. Wednesday-Friday.

June 5-7—**6th Annual Spring Diagnostic Ultrasound Conference.** L.A. Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. 17 hrs. $290. Contact: John Kassabian, MD, 100 Congress St., Pasadena 91105.

June 16-19—**Society of Nuclear Medicine.** Hilton, Las Vegas. Tuesday-Friday. 28 hrs. $60, members; $120, nonmembers. Contact: Registrar, SNM, 475 Park Ave. S., New York 10016. (212) 889-0717.

August 16-21—**23rd Annual Postgraduate Course in Dermal Pathology.** Memorial Hospital Medical Center-UCI Center for Health Education at Newporter Inn, Newport Beach.

Sunday-Friday. Contact: Program Coordinator, Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

September 19—**8th Annual Radiology Symposium.** So. Calif. Permanente Medical Group at Hilton Hotel, Los Angeles. Saturday. Contact: Felecia Madison, SCPMG, Education and Research Dept., 4747 Sunset Blvd., 4th Floor, Los Angeles 90027. (213) 667-4516.

Postgraduate Videotape Programs in Diagnostic Radiology. Developed by Dept. of Radiology, UCSF. 27 programs in all aspects of diagnostic radiology. Outstanding national and international guest lecturers in addition to UC staff present basic approaches to radiographic interpretation and technique as well as new research and clinical advances. Contact: Radiology Postgraduate Ed. Section, UCSF, Dept. of Rad., Rm. M396, San Francisco 94143. (415) 666-5731, between 7:00 a.m. and 4:00 p.m.

SURGERY

April 23-24—**XII Jules Stein Lecture and Annual Postgraduate Seminar—Anterior Segment Disease: Current Update on Immunology, Corneal Disease, Refractive Surgery, and Contact Lenses.** Jules Stein Eye Institute, Los Angeles. Thursday-Friday. 16 hrs. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024. (213) 825-4617.

April 25—**Radial Keratotomy Workshop.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024. (213) 825-4617.

May 3-4—**6th Annual Clarence E. Stafford Memorial Surgical Symposium and Lecture—Update in Surgery of the Gallbladder and Biliary Tract.** White Memorial Medical Center and LLU at Hilton Hotel, Los Angeles. Sunday-Monday. 16 hrs. $200. Contact: Dir., Cont. Med. Ed., White Mem. Med. Ctr., 1720 Brooklyn Ave., Los Angeles 90033. (213) 268-5000, ext. 1460.

May 5-8—**2nd Annual Verne T. Inman Lectureship and 16th Annual Scientific Program of the LeRoy C. Abbott Orthopaedic Society.** UCSF. Tuesday-Friday. 14 hrs. Contact: Eileen Gaines, Alumni Sec., UCSF, U 471, San Francisco 94143. (415) 666-1166.

May 9-16—**Management of the Surgical Patient.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 25 hrs. $295.

May 21-22—**Neurosurgery—11th Annual Postgraduate Course.** UCSF. Thursday-Friday.

May 21-23—**Retina Workshop.** St. Mary's Hospital and Medical Center at Quail Lodge, Carmel Valley. Thursday-Saturday. 12 hrs. Contact: Retina Research Fund, St. Mary's Hosp. and Med. Ctr., 450 Stanyan St., San Francisco 94117.

May 22-23—**Vitrectomy-Ocutome Workshop.** PMC. Friday-Saturday. 12 hrs. $450.

May 30—**The Child With Facial Deformity: A Progress Report.** Plastic Surgery Research Foundation and Children's Hospital and Health Center of San Diego at Vacation Village, San Diego. Saturday. 8 hrs. $75. Contact: Karen Delaney, Plastic Surgery Research Fndn., P.O. Box 33387, San Diego 92103. (714) 272-3126.

June 1-5—**Intensive Course in Refractive Keratoplasty: Barraquer Technique.** Jules Stein Eye Institute, Los Angeles. Monday-Friday. $1,500. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024.

June 5-6—**Ophthalmology Update.** UCD, PMC, UCSF, STAN at Sheraton-Palace, San Francisco. Friday-Saturday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062.

June 6-12—**Orthopaedic Review Course.** UCSF at Golden Gateway Holiday Inn, San Francisco. One week.

June 20-27—**Ophthalmology.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. $350.

June 26-27—**Surgery Trauma.** UCLA. Friday-Saturday.

September 18-19—**Ophthalmology Update.** UCD, PMC, UCSF, STAN at Sheraton-Palace, San Francisco. Friday-Saturday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062.

September 19—**Oxygen Transmission and Extended Wear Contact Lenses.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024.

OF INTEREST TO ALL PHYSICIANS

April 23-25—**Postgraduate Institute.** CMA at Ahwahnee Hotel, Yosemite. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

April 23-26—**Wound Management Workshop.** UCSD at Hilton, San Diego. Thursday-Sunday. 20 hrs.

April 25-26—**Pharmacokinetics '81.** Memorial Hospital Medical Center—UCI Center for Health Education, Long Beach. Saturday-Sunday. Contact: Prog. Coordinator, Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

April 25-May 2—**Diagnostic and Therapeutic Skills.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $350.

May 1-2—**Annual Spring Seminar.** Providence Hospital at Claremont Hotel, Oakland. Friday-Saturday. Contact: Providence Hosp., Med. Staff Office, Box 23020, Oakland 94623. (415) 874-8003.

May 5-11—**Basic Diving Medicine.** UCSF at Fresno and Monterey. One week.

May 7-8—**Advances in Infectious Diseases—Sexually Transmitted Diseases in Clinical Practice.** UCSF. Thursday-Friday.

May 11-15—**Postgraduate Institute for Primary Care Physicians—Symposium on Non-Emergency Outpatient Care.** UCSD at Vacation Village, San Diego. Monday-Friday. 27 hrs. $275.

May 16—**Otolaryngology for the Primary Care Physician.** Institute for Medical Education and Research and UCSD at Cafe del rey Moro, San Diego. Saturday. 8 hrs. $70. Contact: Karen Delaney, Inst. for Medical Education and Research, 135 Dickinson St., San Diego 92103. (714) 272-3126.

May 16-17—**Eating Disorders.** UCLA. Saturday-Sunday.

May 17-22—**Fingers-to-the-Toes: An Orthopedic Approach for the Family Physician.** UCD at Stanford Sierra Lodge, Fallen Leaf Lake. Sunday-Thursday.

May 20—**Asbestos-Related Disease: An Occupational Health Forum for Health Professionals.** Western Institute for Occupational/Environmental Sciences and Herrick Hospital at Veterans Building, San Francisco. Wednesday. Contact: Jane Riggan, Western Inst. for Occupational/Environmental Sciences, 2520 Milvia, Berkeley 94704. (415) 845-6476.

May 30—**Alternative Treatments for Chronic Disease: Integration With Traditional Medical Practice.** PMC. Saturday. 6 hrs. $100.

May 31-June 6—**Family Practice Refresher Course.** UCLA at Miramar-Sheraton, Santa Monica. One week.

June 1-5—**8th Annual Family Practice Refresher Course.** UCLA and Santa Monica Hospital Medical Center at Miramar-Sheraton, Santa Monica. Monday-Friday. 37 hrs. $350. Contact: UCLA.

June 7-13—**Family Practice Refresher Course.** UCI at Disneyland Hotel, Anaheim. One week. 53 hrs. Contact: Cont. Ed. in Health Sciences, UCI Extension, P.O. Box AZ, Irvine 92716. (714) 833-5414.

June 8-12—**Family Practice Board Review Course.** UCSF. Monday-Friday.

June 10-12—**6th Annual Conference on Hyperbaric Oxygen.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. Contact: Program Coordinator, Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

June 11-13—**Human Sexuality.** CMA at Claremont Resort, Oakland. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

June 12-14—**Clinical Update.** American Medical Association at Hilton, San Francisco. Friday-Sunday. Contact: AMA Dept. of Meeting Services, 535 N. Dearborn St., Chicago 60610. (312) 751-6000.

June 26—**Occupational Safety and Health for Hospitals: Keeping a Safe and Healthy Workplace.** PMC. Friday. 6 hrs. $50.

June 28-30—**Family Problems, Aging and Sexuality.** USC. Sunday-Tuesday. 17¼ hrs. $136.

August 8-15—**Reproductive Endocrinology, Infertility and Contraception—3rd Annual Course.** USC at Royal Lahaina Hotel, Maui, Hawaii. One week. 21½ hrs. $325.

August 16-21—**9th Annual Family Practice Refresher Course.** UCD at Hyatt Del Monte, Monterey. Sunday-Friday. 36 hrs.

August 29-September 5—**Concepts in Infertility—1981—Fifth Annual Edward Tyler Symposium.** Tyler Medical Clinic and Univ. of Hawaii School of Medicine at Royal Lahaina Hotel, Maui, Hawaii. One week. Contact: Frank De Llyls, Astra Tours and Travel, 10929 Weyburn Ave., Los Angeles 90024. (213) 479-4444.

September 7-18—**Intensive Residency in Occupational Medicine, Session III.** UCSF. Two weeks.

September 21-24—**American Academy of Family Physicians.** Convention Center, Las Vegas. Monday-Thursday. 30+ hrs. Contact: Edward E. Daleske, Sec., Committee on Scientific Programs, AAFP, 1740 W. 92nd St., Kansas City, MO 64114. (816) 333-9700.

October 12-14—**Interpretative Enzymology.** UCSD at Sheraton Airport Hotel, San Diego. Monday-Wednesday.

October 12-16—**Hawaii Medical Association—Annual Meeting.** Ilikai Hotel, Honolulu. Monday-Friday. Contact: HMA, 320 Ward Ave., Honolulu 96814. (808) 536-7702.

October 18-23—**Recognition and Management of Diving Casualties.** UCSD at Travelodge, Harbor Island, San Diego. Sunday-Friday.

October 28-30—**Workshops in Clinical Hypnosis.** USCD at Village Inn, La Jolla. Wednesday-Friday.

Needs Identification and Fulfillment Tailored to the Individual (NIFTI). UCSF. A new contemporary approach to formal continuing medical education. Participating physicians identify their own CME needs which will be met by a program specifically tailored by UCSF faculty for each individual physician. 25 hrs. minimum; 100, maximum. Fee: $350; $200, UCSF alumni. Contact: Extended Programs in Medical Education, 569-U, Univ. of Calif., San Francisco 94143. (415) 666-4251.

Audio-Digest Foundation—A nonprofit subsidiary of CMA. Provides by subscription twice-a-month tape recorded summaries of leading national meetings and authoritative surveys of current literature. A catalog of lectures and panel discussions in all areas of medical practice is also available. Contact: Audio-Digest Foundation, 1577 E. Chevy Chase Dr., Glendale 91206.

Videotape Postgraduate Course for the Primary Care Physician. UCSF, School of Medicine, Div. of Ambulatory and Community Medicine. 24 Category I hrs. upon completion of course as designed—12 programs each year. Contact: Ms. Estelle Nelson, UCSF, Rm. 432-A, 400 Parnassus Ave., San Francisco 94143. (415) 666-1445.

The UCI Family Practice Refresher Course

Presented for the 24th time

6 meetings — Monday, June 8th through Saturday, June 13th

Offered in preparation for examination for certification by American Board of Family Practice. Program acceptable for 47 hours (can lead to maximum of 53 by American Academy of Family Physicians).

Fee: $445
Disneyland Hotel
Block of rooms reserved until May 17
$58 single, $64 double, $70 triple.

Course Coordinator
Leonard G. Paul, M.D.
Associate Clinical Professor, Department of Family Medicine

For details call (714) 833-5414
(Visa or Mastercharge accepted)

University of California, Irvine
UCI Extension

ALASKA, MONTANA and IDAHO

This list of continuing education programs in Alaska, Montana and Idaho is supplied by the University of Washington School of Medicine's program of regional medical education in Washington, Alaska, Montana and Idaho (WAMI). To have events listed, please send information to: WAMI Program, CME Calendar, D-207 Health Sciences Building, School of Medicine, SC-64, University of Washington, Seattle, Washington 98195; or phone (206) 543-6995.

ALASKA

April 30—**Group Therapy—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday, 7:30 pm-9:30 pm. Alaska Psychiatric Institute Medical Library. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99503. (907) 274-7579.

May 27—**Univ. of Wash. Ob/Gyn Session** (Anchorage). Wednesday, 12-1 p.m. Providence Hospital. Contact: Hedric Hanson, MD, 3300 Providence Drive, Anchorage, AK 99504. (907) 276-8385.

June 18—**Consultation on Adolescent Problems/Systems Approach—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday, 7:30 pm-9:30 pm. Alaska Psychiatric Institute Medical Library. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99503. (907) 274-7579.

MONTANA

April 15—**Pediatric Psychiatry—Univ. of Wash. Pediatrics Sessions** (Great Falls). Wednesday. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

April 22-24—**Congenital Heart Disease in Adults—Univ. of Wash. Internal Medicine Review Sessions.**

April 22, Wednesday, Great Falls. 5-7:30 p.m., Deaconess Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

April 23, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: D. Frank Johnson, MD, Marillac Hall, Billings, MT 59101. (406) 657-7083.

April 24, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

May 27-29—**Office Endocrinology—Univ. of Wash. Internal Medicine Review Sessions.**

May 27, Wednesday, Great Falls. 5-7:30 p.m. Columbus Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

May 28, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: D. Frank Johnson, MD, Marillac Hall, Billings, MT 59101. (406) 657-7083.

May 29, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

June 10—**Allergy—Univ. of Wash. Pediatrics Sessions** (Great Falls). Wednesday. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

IDAHO

May 18—**Evaluation and Treatment of Premature Labor—Univ. of Wash. Ob/Gyn Sessions** (Boise). Monday. 12-1 p.m., St. Luke's Hospital. Contact: David M. Barton, MD, 999 N. Curtis Rd., Boise, ID 83706. (208) 385-9391.

May 19—**Psychiatry—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12-1 p.m., St. Anthony Hospital. Contact: David Fischel, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

NEW MEXICO

All courses listed below have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the Amercan Medical Association. The Continuing Medical Education Committee of the New Mexico Medical Association has certified all courses listed below as meeting the criteria for Category 4 under the New Mexico Board of Medical Examiners Continuing Medical Education regulations.

Information and requests for accreditation should be sent to the chairman of the CME Committee, New Mexico Medical Society, 2650 Yale SE No. 105, Albuquerque, NM 87106 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 247-0539.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

April 23—**Annual OB/GYN Advances in Patient Care Meeting.** Albuquerque. Thursday. Four Seasons Motor Inn. 6 credit hours, also AAFP Prescribed. Contact: CME Office, UNM School of Medicine, Albuquerque, NM 87131. (505) 277-3942.

April 24-26—**Pulmonary Medicine Seminar.** Abiquiu. Friday-Sunday. Ghost Ranch. 15 credit hours. Contact: New Mexico Chapter, American College of Physicians, 2650 Yale S.E. #105, Albuquerque, NM 87106. (505) 247-0539.

April 30-May 2—**Arrythmia Diagnosis and Management for the Noncardiologist.** Santa Fe. Thursday-Saturday. Inn at Loretto. 18 credit hours, also AAFP Prescribed. Contact: Glenn J. Gray, c/o Barry Ramo, MD, 201 Cedar SE #604, Albuquerque, NM 87102. (505) 242-2796.

May 1-2—**Nephrology '81 Calcium and the Kidney—"Stones, Bones and Renes."** Albuquerque. Friday-Saturday. Savage Auditorium, Presbyterian Professional Building. 6 credit hours. Contact: National Kidney Foundation of NM, 530 Jefferson NE, Albuquerque, NM 87108. (505) 266-4573.

May 6-8—**New Mexico Medical Society Annual Meeting—Critical Care for the Community Hospital.** Albuquerque. Wednesday-Friday. Hilton Inn. 10 credit hours, also AAFP Prescribed. Contact: New Mexico Medical Society, 2650 Yale SE, Albuquerque, NM 87106. (505) 247-0539.

May 8-10—**Ambulatory Care in OB/GYN—American College of OB/GYN Postgraduate Course.** Albuquerque. Friday-Sunday. Hilton Inn. 16 credit hours, also AAFP Prescribed. Contact: Registrar, ACOG, One E. Wacker Dr., Ste. 2700, Chicago, IL.

May 9-10—**New Mexico/El Paso Chapter, American College of Surgeons Annual Meeting.** Albuquerque. Saturday-Sunday. Hilton Inn. 11 credit hours. Contact: Brian Miscall, MD, Program Chairman, #25, 801 Encino Pl. NE, Albuquerque, NM 87102. (505) 842-8016.

May 15—**New Techniques in Diagnostic Imaging and Radiotherapy.** Albuquerque. Friday. Four Seasons Motor Inn. 4

credit hours. Contact: CME Office, UNM School of Medicine, Albuquerque, NM 87131. (505) 277-3942.

May 15-16—**Pediatric Cardio-Pulmonary Update Symposium.** Albuquerque. Friday-Saturday. Convention Center. 10 credit hours. Contact: Steven Yabek, MD, Dept. of Pediatrics, UNM School of Medicine, Albuquerque, NM 87131. (505) 277-4361.

June 2—**Comprehensive Care of the Cardiac Patient.** Alamogordo. Tuesday. Gerald Champion Hospital. 5 credit hours. Contact: Franklin D. Ashdown, MD, Gerald Champion Hospital, Alamogordo, NM. (505) 437-3770.

June 25-27—**Oxygen Transport to Human Tissues—A Symposium in Honor of Dr. U. C. Luft.** Albuquerque. Thursday-Saturday. Lovelace Medical Center. 16.5 credit hours. Contact: Waneta C. Tuttle, PhD, Lovelace Medical Foundation, 5400 Gibson SE, Albuquerque, NM 87108. (505) 832-7155.

July 20-23—**Ruidoso Family Practice Seminar.** Ruidoso. Monday-Thursday. Inn of the Mountain Gods. 18 credit hours, also AAFP Prescribed. Contact: Convention Director, P.O. Box 456, Sunland Park, NM 88063. (505) 247-0539.

July 22-25—**Current Concepts in the Surgical Pathology of the Thyroid, Parathyroid, Thymus and Mediastinum.** Santa Fe. Wednesday-Saturday. Santa Fe Hilton. 15 credit hours. Contact: Symposia de Santa Fe, 465 St. Michaels Dr., Santa Fe, NM 87501. (505) 982-1911.

September 3-5—**Sports Medicine.** Albuquerque. Thursday-Saturday. Location to be announced. 10 credit hours. Contact: Otto Appenzeller, MD, Dept. of Neurology, UNM School of Medicine, Albuquerque, NM 87131. (505) 277-3342.

September 27-October 1—**Southwest Obstetrical & Gynecological Society 1981 Annual Meeting.** Santa Fe. Sunday-Thursday. Inn at Loretto. 30 credit hours, also AAFP Prescribed. Contact: W. Duane McCarty, MD, 5400 Gibson SE, Albuquerque, NM 87108. (505) 842-7291.

OREGON

This bulletin of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

University of Oregon Medical School, Department of Psychiatry, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, University of Oregon Medical School. Contact: Dept. of Psychiatry, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8144.

University of Oregon Medical School, Department of Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, University of

The Thyroid Disease Diagnostic Center of

THE HOSPITAL of the GOOD SAMARITAN

presents

the fourth annual

THYROID '81

WEDNESDAY

MAY 6, 1981

Los Angeles Bonaventure

Distinguished Faculty

ELAINE M. KAPTEIN, MD ..... *Los Angeles, CA*
GEORGE R. LEOPOLD, MD ..... *San Diego, CA*
ERNEST L. MAZZAFERRI, MD ..... *Reno, NV*
JORGE H. MESTMAN, MD ..... *Los Angeles, CA*
JOHN T. NICOLOFF, MD ..... *Los Angeles, CA*
PETER A. SINGER, MD ..... *Los Angeles, CA*
DAVID H. SOLOMON, MD ..... *Los Angeles, CA*
ROGER TERRY, MD ..... *Los Angeles, CA*
Course Director: PETER A. SINGER, MD

Fees: (Luncheon Incl.) $70 MDs • $30 Interns, Residents, Fellows, Retired MDs, other allied health professionals

This course is acceptable for up to 7 hours Category I Credit towards CMA and AMA certificates in Continuing Medical Education.

Registration for THYROID '81 May 6, 1981

Name _____

Specialty _____ Phone _____

Address _____

City _____ Zip _____

Make check payable to: THYROID '81

Mail check and registration form to:

THYROID '81
Hospital of the Good Samaritan
616 So. Witmer Street
Los Angeles, CA 90017

For more information:

MARY JANE THOMPSON
Coordinator of Symposia
(213) 977-2345

Oregon Medical School. Contact: Dept. of Medicine, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8607.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, OR 97213. (503) 234-8211.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00-9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee, P.O. Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

EMERGENCY MEDICINE

June 4-6—**Update: Emergency Medicine.** Sponsored by the Oregon Chapter of ACEP, EDNA and OSEMTA. Thursday-Saturday. Salishan Lodge, Gleneden Beach, Oregon. For additional information please contact: Vivian Curry, c/o E/PCP Program, Good Samaritan Hospital & Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7711.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center, Portland. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-7590.

OBSTETRICS AND GYNECOLOGY

October 1-3—**Pacific Northwest Review of Obstetrics & Gynecology.** Thursday-Saturday. Thunderbird-Jantzen Beach, Portland, Oregon. For additional information please contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, Portland, OR 97201. (503) 226-1555.

INTEREST TO ALL PHYSICIANS

September 11-12—**Ashland Conference: Gastroenterology.** Friday-Saturday. Ashland Hills Inn, Ashland, Oregon. For additional information please contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, Portland, OR 97201. (503) 226-1555.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. Please send information to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle 98121; or phone (206) 623-4801.

April 1, 8, 15 & 29—**Medicine & Society In History.** U/W Waterfront Activities Center. Seattle. Wednesdays. 5:30-9:00 p.m. Contact: U/W School of Medicine.

April 18—**The Medical Consequences of Nuclear Weapons & Nuclear War.** U/W Meany Hall. Seattle. Saturday. Contact: U/W School of Medicine.

April 18-25—**Emergency Medical Care.** Maui, Hawaii. Saturday-Saturday. U/W at Wailea Beach, Maui, Hawaii. Contact: U/W School of Medicine.

April 27—**Total Parenteral Nutrition—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

April 30-May 2—**Trauma.** Seattle. Thursday-Saturday. Contact: U/W School of Medicine.

May 1—**Management of Acute Medical Problems.** Seattle. Friday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

May 6—**Medicine & Society in History.** U/W Waterfront Activities Center. Seattle. Wednesdays. 5:30-9:00 p.m. Contact: U/W School of Medicine.

May 7-8—**Medical Genetics and Teratology.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

May 8-9—**Washington Academy of Family Physicians Annual Scientific Program.** Yakima. Friday-Saturday. Yakima Convention Center. Contact: Carolyn Palmer, 3700 140th Avenue NE, Bellevue, WA 98005. (206) 883-8852.

May 15—**Medical Alumni: Medicine, Mankind and the Mountain.** Seattle. Friday. Contact: U/W School of Medicine.

May 18—**Arrhythmias—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

May 19—**Evaluation and Treatment of Premature Labor—Univ. of Wash. OB/GYN Sessions.** (Spokane). Tuesday. 12-1 p.m., Sacred Heart Medical Center. Contact: Wm. Harvey Frazier, MD, West 101 8th Ave., Spokane, WA 99204. (509) 838-8347.

May 22-23—**Northwest Academy of Otolaryngology and Head and Neck Surgery Annual Scientific Program.** Seattle. Friday-Saturday. Washington Athletic Club. Contact: C. Thomas Yarington, MD, The Mason Clinic, 1100 Ninth Avenue, Seattle, WA 98101. (206) 223-6833.

May 22-24—**Comprehensive Care for Physically Disabled Children.** Seattle. Friday-Sunday. Washington Plaza. Contact: John A. Hinckley, AACPDM, PO Box 11083, Richmond, VA 23230. (804) 355-0147.

May 23-30—**Allergy and Immunology.** Maui, Hawaii. Saturday-Saturday. U/W at Wailea Beach, Maui, Hawaii. Contact: U/W School of Medicine.

May 29-30—**Northwest Association of Physical Medicine and Rehabilitation.** Friday-Saturday. Seattle. Washington Plaza Hotel. Contact: Eugen Halar, MD, Seattle VA Medical Center, RMS (117), 4435 Beacon Avenue South, Seattle, WA 98108. (206) 762-1010, Ext. 138.

COURSE SPONSORS AND CONTACT INFORMATION

CME PIERCE COUNTY—Contact: Mrs. Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON) — Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Sandra McDonald, Division of Continuing Medical Education, Virginia Mason Medical Center, 1100 Ninth Avenue, Seattle, WA 98101. (206) 223-6898.

June 4-5—**Pacific Northwest Chapter of the American College of Chest Physicians: Cardiopulmonary Symposium.** Seattle. Thursday-Friday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

June 9—**Pediatric Allergy—Univ. of Wash. Pediatrics Sessions** (Spokane). Tuesday. 12-1 p.m., Sacred Heart Medical Center. Contact: Frank Reynolds, MD, WAMI Office, 3 North, Sacred Heart Medical Center, Spokane, WA 99204. (509) 455-8220.

June 11-12—**Regional Anesthesia and Nerve Block.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

June 15-19—**Death Investigation.** Seattle. Monday-Friday. Contact: U/W School of Medicine.

June 15—**Antibiotic Update.** Sacred Heart Medical Center. Spokane. Monday. Contact: U/W School of Medicine.

June 16—**Antibiotic Update.** U/W Health Sciences Building. Seattle. Tuesday. Contact: U/W School of Medicine.

June 18-19—**Respiratory Care.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

June 18-20—**Modern Office Procedures: Minor Surgeries.** Seattle. Thursday-Saturday. Contact: U/W School of Medicine.

June 22—**Ophthalmology for the Internist—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

July 19-27—**Alaska Cruise: OB/GYN.** Sunday-Monday. Contact: U/W School of Medicine.

July 24-26—**Washington State Society of Anesthesiologists: Seafair III Anesthesia Meeting.** Seattle. Friday-Sunday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

July 27-31—**Psychiatry & The Behavioral Sciences: The 1980s.** Bayshore Inn. Vancouver, British Columbia. Monday-Wednesday and Friday. Contact: U/W School of Medicine.

August 5-7—**Great Debates in Otolaryngology.** Seattle. Wednesday-Friday. Contact: U/W School of Medicine.

August 21-28—**Alaska Cruise: Radiology.** Friday-Friday. Contact: U/W School of Medicine.

August 21-28—**Alaska Cruise: Strabismus.** Friday-Friday. Contact: U/W School of Medicine.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the Academy for Continuing Medical Education, a foundation of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Academy for Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the Academy at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the Academy for current details.

GRAND ROUNDS

SPONSOR: Primary Children's Medical Center
TITLE: **Pediatric Grand Rounds**
LOCATION: PCMC
DATE: First and third Thursdays—8:00 a.m.
CONTACT: Cathy Van Komen (801) 363-1221
SPONSOR: Utah Valley Hospital, Provo
TITLE: **Interdepartmental Grand Rounds**
LOCATION: UVH
CONTACT: Gary Watts, MD (801) 373-7850 (Ext. 2143)

* * *

April 17

SPONSOR: Academy for Continuing Medical Education
TITLE: **First Intermountain Conference on CME**
LOCATION: TriArc Travel Lodge, Salt Lake City
FEE: $50.00 (attendance limited to 100)
CREDIT: 7 hours (certified by University of Utah College of Medicine)
CONTACT: Pam Hanson, ACME (801) 355-5290

April 27-May 5

SPONSOR: University of Utah
TITLE: **The London Knee Course**
LOCATION: London, England
FEE: To be announced
CREDIT: 26 hours
CONTACT: Kent M. Samuelson, MD (801) 581-7601

June 3-6

SPONSOR: University of Utah
TITLE: **7th Boston Lacrimal Course**
LOCATION: Holiday Inn, Park City
FEE: To be announced
CREDIT: 20 hours
CONTACT: Darrell E. Wolfley, MD (801) 363-3355

June 11-12

SPONSOR: Castleview Hospital
TITLE: **5th Annual Castle Country Symposium** (with Rock Art Jeep Safari—6-13)
LOCATION: Price
FEE: $75.00
CREDIT: 12 hours
CONTACT: Mary Louise Ghirardelli (801) 637-4800

SPONSORS OF COURSES—ABBREVIATIONS

AF: Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.
CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.
CWH: Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461
FHP: Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.
HAFB: Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.
HCH: Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.
LDSH: Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.
MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.
OEH: Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.
OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409
PCMC: Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.
SHCC: Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.
SLSC: Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.
UAFP: Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.
UUMC: University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.
UVH: Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.
VAMC: Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—4107 Laurel St., Anchorage 99504. Annual Meeting: May 23-27, 1981, Glacier Bay Lodge, Glacier Bay.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. Annual Meeting: May 20-24, 1981, The Pointe Resort, Phoenix.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: March 12-17, 1982, Disneyland Hotel, Anaheim.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. Annual Meeting: September 9-12, 1981, Keystone.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. Annual Meeting: October 12-16, 1981, Ilikai Hotel, Honolulu.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. Annual Meeting: July 23-26, 1981, Sun Valley.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Annual Meeting: October 1-3, 1981, Copper King Inn, Butte.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. Annual Meeting: May 15-17, 1981, Carson City.

New Mexico Medical Society—2650 Yale SE, Albuquerque 87106. Annual Meeting: May 6-8, 1981, Hilton Inn, Albuquerque.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. Annual Scientific Session: October 29-30, 1981, Portland.

Utah State Medical Association—540 East Fifth South St., Salt Lake City 84102. Annual Meeting: September 8-11, 1981, Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. Annual Meeting: September 24-27, 1981, Davenport Hotel, Spokane.

Wyoming State Medical Society—P.O. Drawer 4009, Cheyenne 82001. Annual Meeting: June 22-26, 1981, Ramada Snow King Inn, Jackson.

June 15-19

SPONSOR: University of Utah Rocky Mountain Center for Occupational and Environmental Health
TITLE: **Occupational Safety and Health in the Mining Industry**
LOCATION: Salt Lake City
FEE: To be announced
CREDIT: To be announced
CONTACT: Katharine Blosch (801) 581-5710

June 17-19

SPONSOR: University of Utah
TITLE: **Society for Epidemiologic Research**
LOCATION: Snowbird
FEE: To be announced
CREDIT: 22.5 hours
CONTACT: Joseph L. Lyon, MD (801) 581-5270

June 22-25

SPONSOR: University of Utah
TITLE: **Alcoholism and Other Drug Dependencies**
LOCATION: University Medical Center, Classroom C
FEE: To be announced
CREDIT: 28 hours
CONTACT: James R. Swenson, MD (801) 581-7985

October 9

SPONSOR: University of Utah
TITLE: **Regional Joint ACP-ASIM Meeting Topics in Pharmacology**
LOCATION: Salt Lake Hilton
FEE: $20.00
CREDIT: To be announced
CONTACT: Gregory A. Schwitzer, MD (801) 581-7818

November 6

SPONSOR: LDS Hospital
TITLE: **Postgraduate Course—Renal/Pulmonary Syndromes**
LOCATION: Hotel Utah, Salt Lake City
FEE: To be announced
CREDIT: To be announced
CONTACT: C. DuWayne Schmidt, MD (801) 350-1813

Note: Dates, times, places and programs are subject to change on occasion. Please check with the sponsoring organization or the Academy for details.

Index to
The Western Journal of Medicine Advertising

ARTHRITIS FOUNDATION 12
AYERST LABORATORIES
Premarin 16, 17, 18
BRISTOL LABORATORIES
Tegopen 40, 41, 42
BRITISH MEDICAL ASSOCIATION CONGRESS
International Clinical Meetings 14
BURROUGHS WELLCOME CO.
Zyloprim 26
CALIFORNIA MEDICAL ASSOCIATION
1981 Postgraduate Institute 48
CALIFORNIA MEDICAL ASSOCIATION'S WORKSHOP
Stress and Coping 42
CLASSIFIED 23, 27, 31, 34, 35
DOCTORS' CO., THE 13
ELI LILLY AND COMPANY
Ceclor 3
HOMES OF HERITAGE 43
HOSPITAL OF THE GOOD SAMARITAN, THE
Symposium-Thyroid '81 53
HOTEL CORPORATION OF HAWAII 22
INSURANCE CORPORATION OF AMERICA 6, 47
INTERNATIONAL MEDICAL EDUCATION CORPORATION
1981 Postgraduate Seminars 43
KEY PHARMACEUTICALS, INC.
Theo-Dur 20, 21, 22
MAUI ELDORADO RESORT 26
NORCAL MUTUAL INSURANCE CO. 39
NORTHRIDGE HOSPITAL FOUNDATION 44
PRESTO FOOD PRODUCTS, INC.
Mocha Mix 40
PROFESSIONAL BUSINESS SOFTWARE 5
PUREPAC PHARMACEUTICAL CO. 33
ROCHE LABORATORIES
Bactrim 24, 25, 26
Dalmane ..... 2nd Cover, 1, 2
Limbitrol 36, 37, 38
Valium ..... 3rd & 4th Covers
SMITH, KLINE & FRENCH CO.
Dyazide 32
E. R. SQUIBB & SONS INC.
Corgard 8, 9, 10
UNIVERSITY OF CALIFONIA/IRVINE
The UCI Family Practice Refresher Course 51
UPJOHN COMPANY, THE
Motrin 28, 29, 30
WESTERN JOURNAL OF MEDICINE, THE
Subscription 30
WYETH LABORATORIES
Ativan 44,45

THE WESTERN Journal of Medicine

VOLUME 134 • NUMBER 5 MAY 1981

379 *Mesothelioma: Current Perspectives* ROY A. TAYLOR, MD, and LLOYD P. JOHNSON, MD

384 *Primary Isolation of a New Strain of the TATLOCK/Pittsburgh Pneumonia Agent* (Legionella micdadei)
ELIZABETH A. DONEGAN, MD; MARLENE M. DEAL, PhD; M. CLAIRE MELANEPHY, BS; LESTER G. CORDES III, MD; C. WAYNE MOSS, PhD; VINCENT G. PONS, MD, and GEORGE F. BROOKS, MD

390 *Abnormal Aminopyrine Metabolism in Patients With Chronic Hepatitis*
GERSHON W. HEPNER, MD; EDWARD PIKEN, MD, and JUAN LECHAGO, MD, PhD

394 *Obstetric Infections* HENRY A. OSTER, MD

MEDICAL PROGRESS

405 *Fibrositis: Misnomer for a Common Rheumatic Disorder* ROBERT M. BENNETT, MD

SPECIALTY CONFERENCE

414 *Ascites*
Participants: KAREN L. LINDSAY, MD; TELFER B. REYNOLDS, MD; JOHN C. HOEFS, MD, and MIGUEL E. SANMARCO, MD

MEDICAL STAFF CONFERENCE

424 *The Great Imitator, Syphilis* Chief Discussant: FAITH FITZGERALD, MD

IMPORTANT ADVANCES IN CLINICAL MEDICINE

433 *Nuclear Medicine—Epitomes of Progress*

EDITORIALS

438 • *Violence by Handguns* • *Ascites* • *Financial Aid for Medical Students*

CASE REPORTS

441 *Autoerythrocyte Sensitization* WILLIAM M. BOEHME, MD, and JOHN E. KURNICK, MD

442 *Gunshot Penetrating Injuries of the Descending Thoracic Aorta*
CHARLES H. DART, Jr, MD; HOWARD E. BRAITMAN, MD, and SOMBOON LARLARB, MD

446 *Lung Involvement in Progressive Vaccinia*
DAVID S. CHUDWIN, MD; MORTON J. COWAN, MD; DIANE W. WARA, MD, and ALAN C. JOHNSON, MD

CORRESPONDENCE

449 • *More HAFE* • *Gastrointestinal Barotrauma* • *Alkalinization Therapy for Tricyclic Antidepressant Overdose; With Reply by Authors* • *Ascorbic Acid and Nutrition* • *Hypokalemia in the Syndrome of Inappropriate Secretion of Antidiuretic Hormone* • *Medical Records as Instruments of Patient Care* • *Correction: Use of Steroids in Burn Care* • *Platelet Dysfunction and Migraines; With Reply by Author* • *Accidental Hypothermia: Hypoglycemia or Hyperglycemia; With Reply by Author*

MEDICAL ETHICS

457 *Croakers' Dilemma—Should Prison Physicians Serve Prisons or Prisoners?*
KIM MARIE THORBURN, MD

INFORMED OPINION

463 *Fourteen Fallacies About Patient Package Inserts* JERE GOYAN, PhD

472 *Book Reviews*

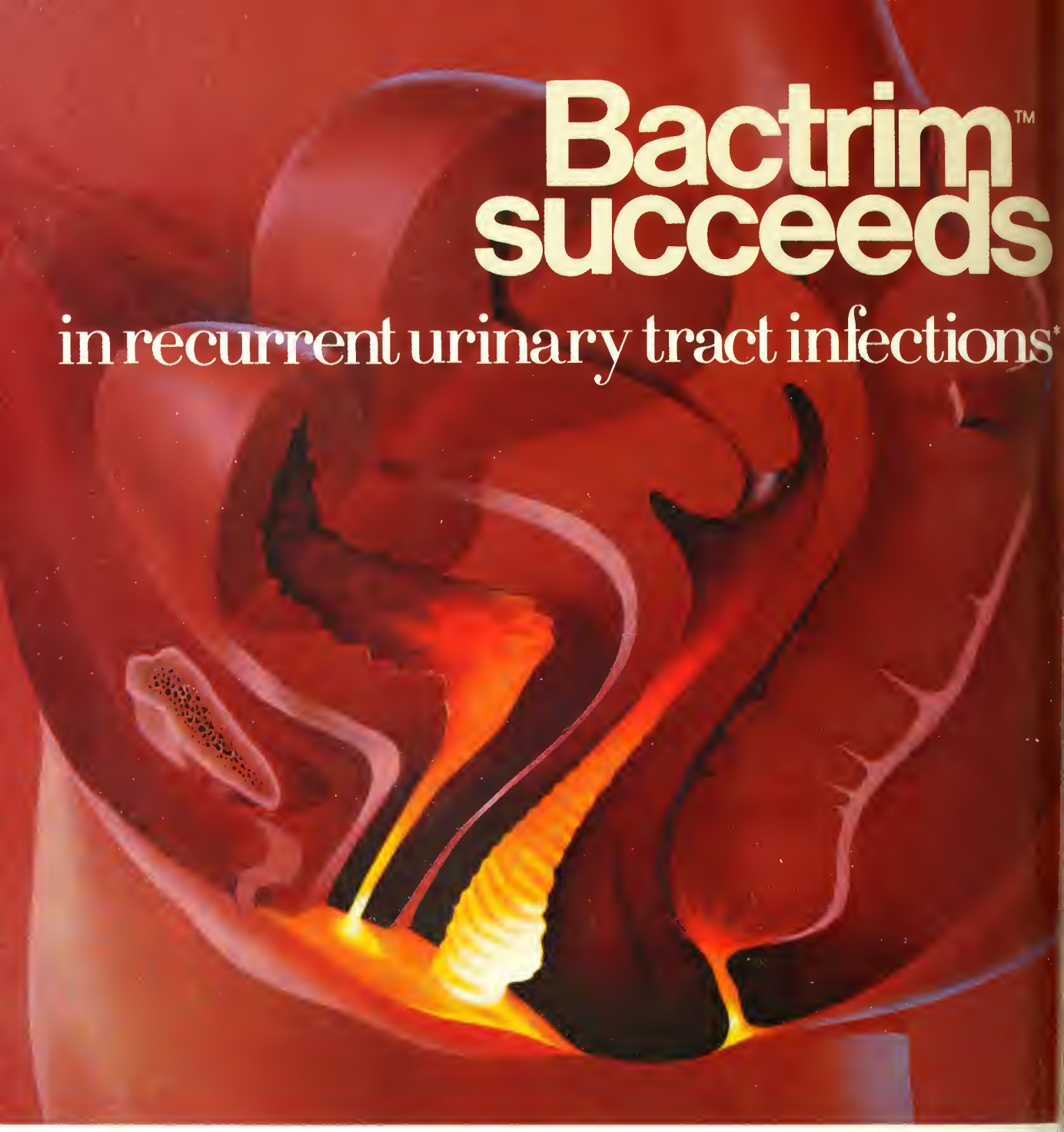
476 *In Memoriam*

Detailed Table of Contents, See Advertising Pages 7 and 11

Information for Authors, See Advertising Page 26

★ **CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA, HAWAII AND NEVADA; ALASKA, MONTANA AND IDAHO; NEW MEXICO; OREGON; WASHINGTON; UTAH**
(See Advertising Page 19)

★★ **Official Journal of the California Medical Association, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association and the Washington State Medical Association**



Bactrim™ succeeds

in recurrent urinary tract infections*

from site to source

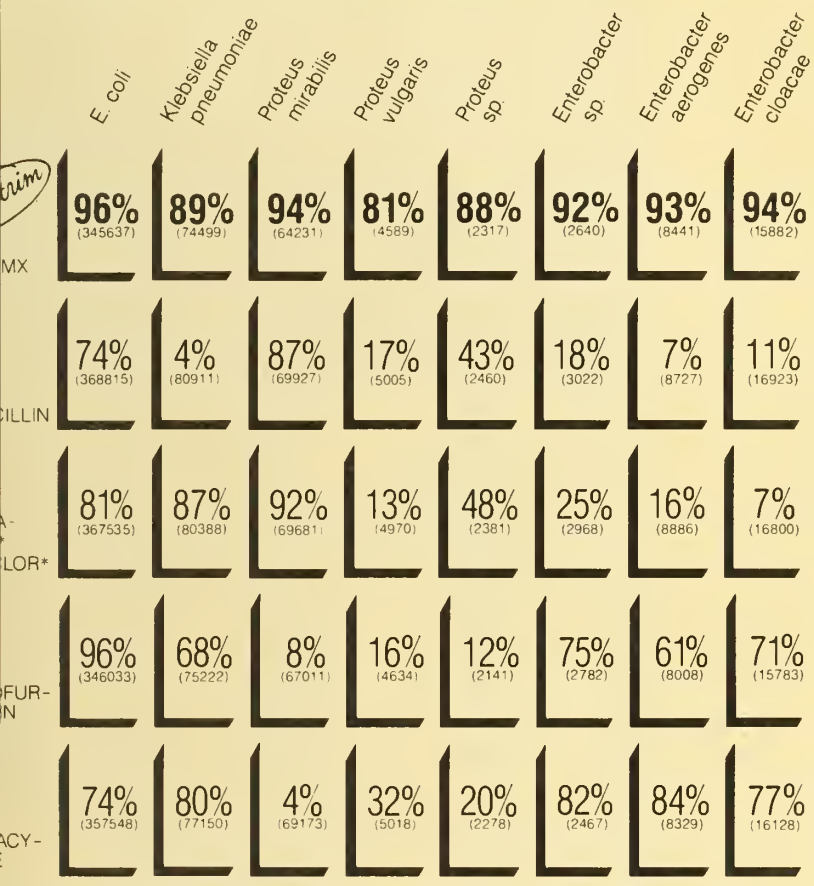
Bactrim reaches effective levels in urine, serum and renal tissue,[1] to combat infection throughout the urinary tract. The trimethoprim component enters vaginal secretions in therapeutic concentrations,[1] to prevent colonization of bacteria in the periurethral area, probably the major etiologic factor in recurrent UTI.[2,3] And in the fecal flora, Bactrim eradicates Enterobacteriaceae with no resulting emergence of resistant organisms and without adverse effect on the normal intestinal flora.

*due to susceptible *E. coli*, *Klebsiella-Enterobacter*, *Proteus mirabilis*, *P. vulgaris* and *P. morgani*

a from 231 hospitals, compiled by an independent bacteriologic monitoring service, show:

ore isolates of more common uropathogens nsitive to Bactrim than to any other equently prescribed antimicrobial

nt of isolates of common uropathogens sensitive to Bactrim and to other antimicrobials



Numbers in parentheses indicate projected number of isolates tested with antibacterial
Source: BacData Medical Information Systems, Inc., Summer 1980.
*Tested with cephalothin disc, recommended as representative of all cephalosporins

Bactrim consistently proves its *in vitro* effectiveness against the organisms estimated to cause 90-95% of urinary tract infections: *E. coli, Proteus mirabilis, Klebsiella* and *Enterobacter* species.[4,5] Susceptibility tests are believed to correlate more closely with clinical results in urinary tract infections than in any other kind.[4]

No significant change seen in resistance patterns

Uropathogens sensitive to Bactrim have demonstrated no significant increased resistance *in vitro* after many years of use in patients with urinary tract infection.[6] In one study,[7] SMX/TMP (Bactrim), given over a period of four weeks, was not followed by emergence of resistant strains of Enterobacteriaceae—a result noted to correlate with clinical findings that in patients given SMX/TMP, urinary tract reinfections with resistant organisms are rare.

It is important to maintain adequate fluid intake during therapy. Bactrim is contraindicated during pregnancy at term, the nursing period, in patients hypersensitive to its components, and in infants under 2 months of age.

References: **1.** Rubin RH, Swartz MN. *N Engl J Med 303* 426-432, Aug 21, 1980. **2.** Dhalla S, Flynn JT. *NY State J Med 80*: 1087-1094, June 1980. **3.** Stamey TA. *J Urol 109* 467-472, Mar 1973. **4.** Kunin CM. *Detection, Prevention and Management of Urinary Tract Infections*, ed 3. Philadelphia, Lea & Febiger, 1979, pp. 91, 140. **5.** Mayer TR. *Geriatrics 35*: 67-77, Mar 1980. **6.** BacData Medical Information Systems, Inc., Winter 1976-1977 to Summer 1980. **7.** Knothe H. *Infection 7* (Suppl 4): S321-S323, 1979.

Bactrim™ DS

160 mg trimethoprim and 800 mg sulfamethoxazole

maximizes results with B.I.D. convenience

ROCHE®

Please see summary of product information on following page.

Bactrim™ DS

160 mg trimethoprim and 800 mg sulfamethoxazole

Before preacribing, pleese consult complete product information, e summery of which follows:

Indications end Usage: For the treetment of urinary trect infections due to susceptible atrains of the following orgenisms: *Escherichie coli, Klebsiella-Enterobacter, Proteus mirebilis, Proteus vulgeris, Proteus morgenii.* it is recommended thet initiel epiaodes of uncompliceted urinary trect infections be treeted with e single effective antibecteriei egent rether then the combination. *Note* The increasing frequency of resistant organisms limits the usefulness of all antibacterials, especially in these urinary tract infections.

For ecute otitis media in children due to susceptible streins of *Heemophilus influenzee* or *Streptococcus pneumoniee* when in physicien's judgment it offers en edventege over other entimicrobiels. Limited clinicei informetion presently aveiiebie on effectiveness of treetment of otitis medie with Bectrim when infection is due to ampiciilin-resistent *Heemophilus influenzae*. To date, there ere iimited dete on the safety of repeeted use of Bectrim in children under two yeers of ege. Bectrim is not indiceted for prophyiectic or proionged administretion in otitis media at eny ege.

For ecute exacerbetions of chronic bronchitis in edults due to susceptible streins of *Heemophilus influenzee* or *Streptococcus pneumoniae* when in physicien's judgment it offers en edventage over e singie entimicrobiai agent.

For enteritis due to susceptible strains of *Shigelle flexneri* and *Shigelle sonnei* when antibacteriai therepy is indiceted.

Aiso for the treetment of documented *Pneumocystis cerinii* pneumonitis. To dete, this drug hes been tested oniy in patients 9 months to 16 yeers of ege who were immunosuppressed by cencer therapy.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides, patients with documented megaloblastic anemia due to folate deficiency; pregnancy at term; nursing mothers because sulfonamides are excreted in human milk and may cause kernicterus; infants less than 2 months of age.

Warnings: BACTRIM SHOULD NOT BE USED TO TREAT STREPTOCOCCAL PHARYNGITIS. Clinical studies show that patients with group A β-hemolytic streptococcal tonsillopharyngitis have higher incidence of bacteriologic failure when treated with Bactrim than do those treated with penicillin. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides. Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended; therapy should be discontinued if a significantly reduced count of any formed blood element is noted.

Precautions: *General.* Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In patients with glucose-6-phosphate dehydrogenase deficiency, hemolysis, frequently dose-related, may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function. Bactrim may prolong prothrombin time in those receiving warfarin; reassess coagulation time when administering Bactrim to these patients. *Pregnancy.* Teratogenic Effects. Pregnancy Category C. Because trimethoprim and sulfamethoxazole may interfere with folic acid metabolism, use during pregnancy only if potential benefits justify the potential risk to the fetus.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. *Blood dyscrasias.* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia; purpura, hypoprothrombinemia and methemoglobinemia. *Allergic reactions.* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal reactions.* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. *CNS reactions.* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous reactions.* Drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia in patients; cross-sensitivity with these agents may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.

Dosege: Not recommended for infents leas then two months of ege.

URINARY TRACT INFECTIONS AND SHIGELLOSIS IN ADULTS AND CHILDREN, AND ACUTE OTITIS MEDIA IN CHILDREN

Adults. Usual adult dosage for urinary tract infections—1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 10-14 days. Use identical daily dosage for 5 days for shigellosis.

Children. Recommended dosage for children with urinary tract infections or acute otitis media—8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, in two divided doses for 10 days. Use identical daily dosage for 5 days for shigellosis.

For patients with renal impairment. Use recommended dosage regimen when creatinine clearance is above 30 ml/min. If creatinine clearance is between 15 and 30 ml/min, use one-half the usual regimen. Bactrim is not recommended if creatinine clearance is below 15 ml/min.

ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS IN ADULTS

Usual adult dosage. 1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 14 days.

PNEUMOCYSTIS CARINII PNEUMONITIS

Recommended dosage: 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours in equal doses every 6 hours for 14 days. See complete product information for suggested children's dosage table.

Supplied: *Double Strength (DS) tablets*, each containing 160 mg trimethoprim and 800 mg sulfamethoxazole, bottles of 100, Tel-E-Dose* packages of 100, Prescription Paks of 20 and 28. *Tablets*, each containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 100 and 500, Tel-E-Dose* packages of 100, Prescription Paks of 40. *Pediatric Suspension*, containing 40 mg trimethoprim and 200 mg sulfamethoxazole per teaspoonful (5 ml), cherry flavored—bottles of 100 ml and 16 oz (1 pint). *Suspension*, containing 40 mg trimethoprim and 200 mg sulfamethoxazole per teaspoonful (5 ml), fruit-licorice flavored—bottles of 16 oz (1 pint).

ROCHE

ROCHE LABORATORIES
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

DOCTORS' SPECIAL!

Give your family a

Condo Vacation in Hawaii

and we'll give you use of a

Car FREE!

When you stay in a 1-bedroom oceanview or 2-bedroom condominium in one of these luxurious resorts, you'll have the use of a car free. All condominiums are on or near the beach and have daily maid service.

WAIKIKI
Island Colony or Waikiki Sunset
Pool, golf nearby and many luxury extras. From $59/day-$370/week
1-4 persons

MAUI
Kaanapali Shores
Free tennis, pool, golf nearby. From $78/day-$490/week
1-4 persons

HAWAII
Kona Lagoon
Free tennis, golf nearby. From $85/day-$535/week
1-4 persons

KAUAI
Pono Kai
Mile-long beach, free tennis, barbecue area, sauna. From $58/day-$365/week
1-4 persons

Serving Hawaii Visitors for More Than 30 Years

hcp HCP Condo Resorts

Andre S. Tatibouet, President
2299 Kuhio Avenue, Honolulu, Hawaii 96815

For reservations, beautiful four-color brochures or information about any of HCP's 18 hotels and condominiums in Hawaii, see your travel agent or call Hawaii Toll Free 800-367-5124.

Call Hawaii Toll Free
800-367-5124

Acute pain is no laughing matter.

The first prescription for the first days of acute pain

Empirin® with Codeine #3

Each tablet contains: aspirin, 325 mg; plus codeine phosphate, 30 mg, (Warning — may be habit-forming). C-III

For the millions of patients who need the potency of aspirin and codeine for their acute pain.

The pain of fractures, strains, sprains, burns and wounds is at its peak during the first three to four days following trauma. The potent action of Empirin with Codeine begins to work within 15 minutes of oral administration, an important advantage during this acute pain period. Empirin with Codeine has unique bi-level action to attack pain at two critical points: peripherally at the site of injury and centrally at the site of pain awareness.

For the most effective dosage in treating acute pain, begin with... two tablets of Empirin with Codeine #2 or #3, every four hours. Titrate downward as pain subsides.

EMPIRIN® with Codeine

C-III

DESCRIPTION: Each tablet contains aspirin (acetylsalicylic acid) 325 mg plus codeine phosphate in one of the following strengths: No 2 — 15 mg, No 3 — 30 mg, and No 4 — 60 mg (Warning — may be habit-forming.)

CONTRAINDICATIONS: Hypersensitivity to aspirin or codeine

WARNINGS:

Drug dependence: Empirin with Codeine can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of this drug and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral, narcotic-containing medications. Like other narcotic-containing medications, the drug is subject to the Federal Controlled Substances Act.

Use in ambulatory patients: Empirin with Codeine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using this drug should be cautioned accordingly.

Interaction with other central nervous system (CNS) depressants: Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics, or other CNS depressants (including alcohol) concomitantly with Empirin with Codeine may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Use in pregnancy: Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, Empirin with Codeine should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

PRECAUTIONS:

Head injury and increased intracranial pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions: The administration of Empirin with Codeine or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Allergic: Precautions should be taken in administering salicylates to persons with known allergies; patients with nasal polyps are more likely to be hypersensitive to aspirin.

Special risk patients: Empirin with Codeine should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture, peptic ulcer, or coagulation disorders.

ADVERSE REACTIONS: The most frequently observed adverse reactions to codeine include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients and some of these adverse reactions may be alleviated if the patient lies down. Other adverse reactions include euphoria, dysphoria, constipation, and pruritus.

The most frequently observed reactions to aspirin include headache, vertigo, ringing in the ears, mental confusion, drowsiness, sweating, thirst, nausea, and vomiting. Occasional patients experience gastric irritation and bleeding with aspirin. Some patients are unable to take salicylates without developing nausea and vomiting. Hypersensitivity may be manifested by a skin rash or even an anaphylactic reaction. With these exceptions, most of the side effects occur after repeated administration of large doses.

DOSAGE AND ADMINISTRATION: Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. Empirin with Codeine is given orally. The usual adult dose for Empirin with Codeine No. 2 and No. 3 is one or two tablets every four hours as required. The usual adult dose for Empirin with Codeine No. 4 is one tablet every four hours as required.

DRUG INTERACTIONS: The CNS depressant effects of Empirin with Codeine may be additive with that of other CNS depressants. See WARNINGS.

Wellcome

Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

THE WESTERN Journal of Medicine

Since 1902 (ISSN 0093-0415)

731 MARKET ST. • SAN FRANCISCO, CA 94103 • TELEPHONE (415) 777-2000

Official Journal of the California Medical Association, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association and the Washington State Medical Association

MALCOLM S. M. WATTS, MD, *Editor*
LLOYD H. SMITH, JR. MD, *Associate Editor*
DAVID GREER, *Managing Editor*
BARBARA T. ROONEY, *Assistant Managing Editor*
VAL BOSMOE, *Editorial Assistant*
MARY JANE MacDWYER, *Copy Editor*
MARY KAY COWANS, *Advertising Production Manager*
KEVIN McKINNEY, *Circulation Coordinator*

editorial communications to DR. WATTS

business communications to MR. GREER

Editorial Board

Chairman of the Board
Malcolm S. M. Watts, San Francisco, Ca

Special Editor for Idaho
E. R. W. Fox, Coeur d'Alene, Id

Special Editor for Nevada
Thomas J. Scully, Reno, Nv

Special Editor for New Mexico
Marcus J. Smith, Santa Fe, NM

Special Editor for Utah
John H. Holbrook, Salt Lake City, Ut

Special Editor for Washington
David Hopkins, Federal Way, Wa

Allergy
Harold S. Novey, Orange, Ca
Abba I. Terr, San Francisco, Ca

Anesthesiology
Ronald L. Katz, Los Angeles, Ca

Cardiac and Thoracic Surgery
John E. Connolly, Irvine, Ca
Albert Starr, Portland, Or

Chest Diseases
Roger K. Larson, Fresno, Ca
Thomas L. Petty, Denver, Co

Dermatology
John H. Epstein, San Francisco, Ca
George F. Odland, Seattle, Wa
Richard B. Stoughton, San Diego, Ca

General and Family Practice
Daniel D. Roberts, Central Point, Or
Harmon E. Holverson, Emmett, Id
Wilfred Snodgrass, Santa Monica, Ca

General Surgery
Fred M. Anderson, Reno, Nv
Daniel T. Cloud, Phoenix, Az
Paul A. Ebert, San Francisco, Ca
Lucius D. Hill, Seattle, Wa
Frank G. Moody, Salt Lake City, Ut

Industrial Medicine and Toxicology
Thomas H. Milby, Berkeley, Ca

Internal Medicine
Robert W. Burroughs, Spokane, Wa
Theodore C. Eickhoff, Denver, Co
Robert L. Hare, Portland, Or
Robert H. Moser, Philadelphia, Pa
George A. Porter, Portland, Or
Helen M. Ranney, San Diego, Ca
David D. Ulmer, Los Angeles, Ca
Edgar Wayburn, San Francisco, Ca
Ralph C. Williams, Jr, Albuquerque, NM

Neurology
Pierre M. Dreyfus, Sacramento, Ca
Philip D. Swanson, Seattle, Wa
W. C. Wiederholt, La Jolla, Ca

Neurosurgery
John R. Green, Phoenix, Az
Arthur A. Ward, Jr, Seattle, Wa
Charles B. Wilson, San Francisco, Ca

Nuclear Medicine
Joseph P. Kriss, Stanford, Ca

Obstetrics and Gynecology
Ralph C. Benson, Portland, Or
Ralph W. Hale, Honolulu, Hi
W. LeRoy Heinrichs, Stanford, Ca
Morton A. Stenchever, Seattle, Wa

Ophthalmology
Robert S. Hepler, Los Angeles, Ca
Bruce E. Spivey, San Francisco, Ca

Orthopedics
Ernest M. Burgess, Seattle, Wa
Duane M. Kline, Jr, Cheyenne, Wy

Otolaryngology
Roger Boles, San Francisco, Ca
Mansfield F. W. Smith, San Jose, Ca

Pathology
Richard L. Kempson, Stanford, Ca

Pediatrics
Louis K. Diamond, San Francisco, Ca
William L. Nyhan, San Diego, Ca
Irving Schulman, Stanford, Ca
Arnold L. Smith, Seattle, Wa

Pharmacology
George N. Aagaard, Seattle, Wa

Physical Medicine and Rehabilitation
Glenn G. Reynolds, San Jose, Ca

Plastic Surgery
Richard P. Jobe, Los Altos, Ca
N. John Wilde, Fresno, Ca

Psychiatry
Carl Eisdorfer, Seattle, Wa
Alan I. Levenson, Tucson, Az
Helen Tausend, Beverly Hills, Ca
Joe Paul Tupin, Sacramento, Ca

Public Health
J. M. Stubblebine, Greenbrae, Ca

Radiology
M. Paul Capp, Tucson, Az
Melvin M. Figley, Seattle, Wa
Marshall Rowen, Orange, Ca

Urology
Richard Middleton, Salt Lake City Ut
Thomas A. Stamey, Stanford Ca

Consulting Editor
Medical Services and Health Care
Paul J. Sanazaro, Berkeley, Ca

POLICY COMMITTEE

BRAD COHN, MD
CHARLES M. HAIR, MD
GLADDEN V. ELLIOTT, MD
SAMUEL HOROWITZ, MD
ROBERT D. BURNETT, MD
THEODORE W. LORING, MD
MALCOLM S. M. WATTS, MD

Advertisements—THE WESTERN JOURNAL OF MEDICINE is published the first week of each month. Advertising copy must be received not later than the first of the month preceding issue. Advertising rates will be sent on request. Acceptance of advertising is contingent upon approval by the Advertising Committee. The journal reserves the right to reject any advertisement.

ADVERTISING SALES REPRESENTATIVES

EAST:
SAUL HORNIK
12 COURT ST.
FREEHOLD, NJ 07728
TEL: (201) 462-8004

MIDWEST:
R. C. JOHNSON & ASSOCIATES
RICHARD C. JOHNSON
547 WEST MELROSE
CHICAGO, IL 60657
TEL: (312) 327-6969

WEST:
MEDIA SERVICES
DARIEN DeLORENZO
LYNNE JEFFES
2612 BELMONT CANYON RD.
BELMONT, CA 94002
TEL. (415) 595-2203
(415) 348-7478

CLASSIFIED:
731 MARKET ST.
SAN FRANCISCO, CA 94103
TEL. (415) 777-2000
(415) 777-0424

Copyright 1981 by the California Medical Association

Owned and Published by the California Medical Association

All material subject to this copyright appearing in THE WESTERN JOURNAL OF MEDICINE may be photocopied for the noncommercial purpose of scientific or educational advancement. Volumes begin with January and July.

The subscription price per year is $10 in the United States and Canada; $18 in all other countries. Single copies are $2. Address all subscription communications to THE WESTERN JOURNAL OF MEDICINE Circulation, 731 Market St., San Francisco, CA 94103.

Allow six weeks for subscriptions to begin. Past issues must be bought individually. So long as reserve stocks are available, missing issue requests from subscribers are honored for up to six months after the issue date. Thereafter, the single copy rate of $2.00 is applicable for each issue available.

Change of Address—Requests for change of address should give both the old and new addresses. Allow six weeks for change-over.

CONTRIBUTIONS OF SCIENTIFIC AND ORIGINAL ARTICLES

Responsibilities for Statements and Conclusions in Original Articles—Authors are responsible for all statements, conclusions and methods of presenting their subjects. These may or may not be in harmony with the views of the editorial staff. It is aimed to permit authors to have as wide latitude as the general policy of the journal and the demands on its space may permit. The right to reduce, revise or reject any manuscript is always reserved.

Exclusive Publication—Articles are accepted for publication on condition that they are contributed solely to this journal. Ordinarily contributors will be notified within 60 days if a manuscript is accepted for publication. Every effort will be made to return unused manuscripts.

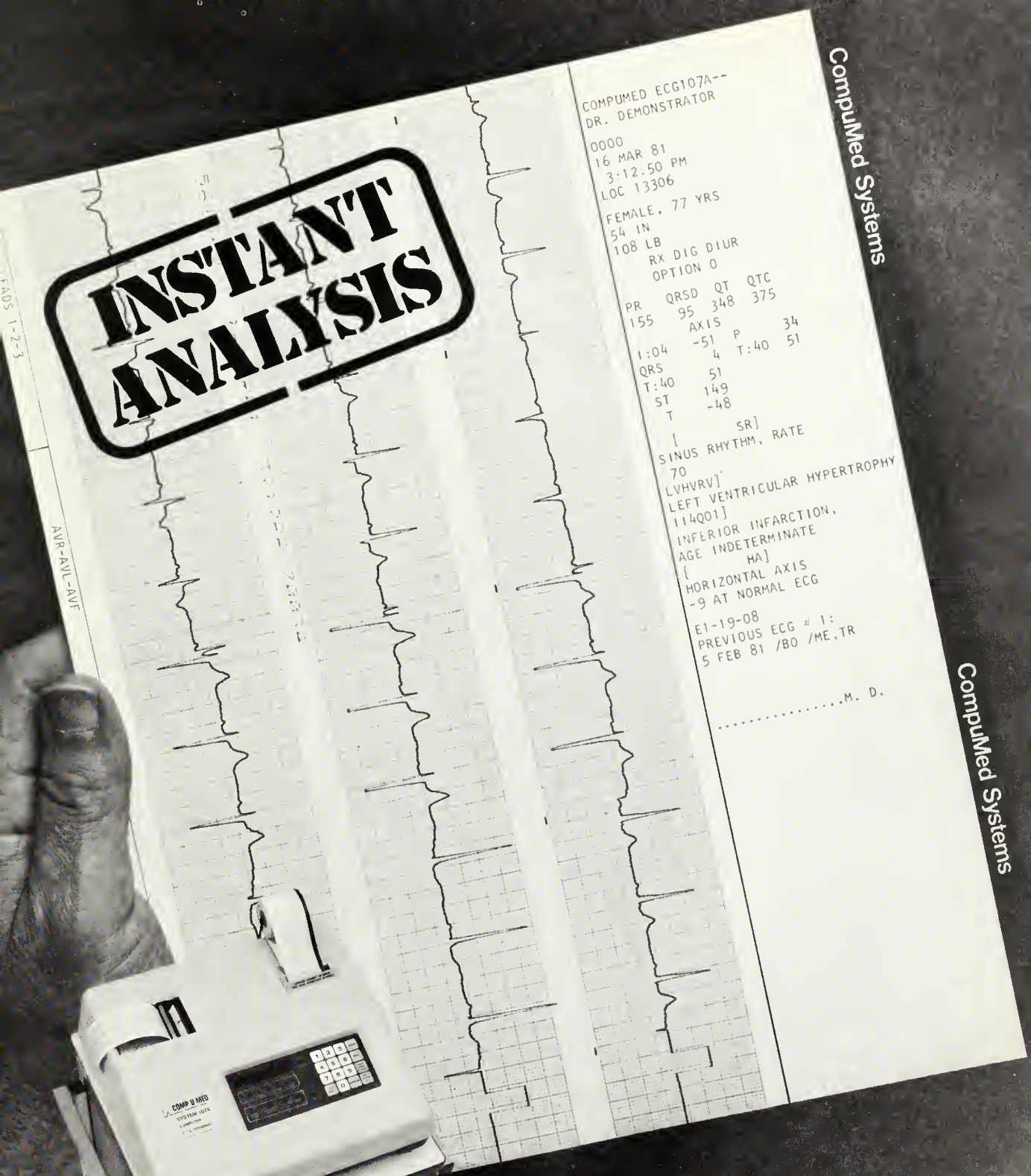
"Information for Authors"—A complete guide to manuscript submission and journal style is available on request and also appears in each January and July issue.

Manuscripts—Ordinarily manuscripts should not exceed 3,000 words (less than 15 typed double-spaced pages). The *original* manuscript and two copies should be submitted, typed double-spaced throughout. If photographic illustrations are desired, three sets of clear, unmounted black and white glossy prints should be supplied. For line drawings, original artwork or glossy prints are acceptable. Tables should be typed on separate sheets of paper.

References—References should conform to the following order: name of author, title of article, name of periodical, and volume with inclusive pages, month and year—i.e., Lee GS: The heart rhythm following therapy with digitalis—In theory and practice. Arch Int Med 44:554-562, Dec 1942. They should be listed in the order in which they are cited in the text, numbered in sequence and punctuated as above.

Reprints—Reprints are available to authors at established standard rates.

"Entered as second class matter at the post office in San Francisco under the Act of March 3, 1879." Acceptable for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized August 10, 1918. Publication Number 084480.



prints complete ECG analysis in your office

Now, an automatic ECG service that produces a complete computer-assisted ECG interpretation is available for the private practitioner. Perfected in major hospitals, the CompuMed System will print–in less than three minutes–an accurate, ECG tracing and interpretation in your own office at an extremely low cost.

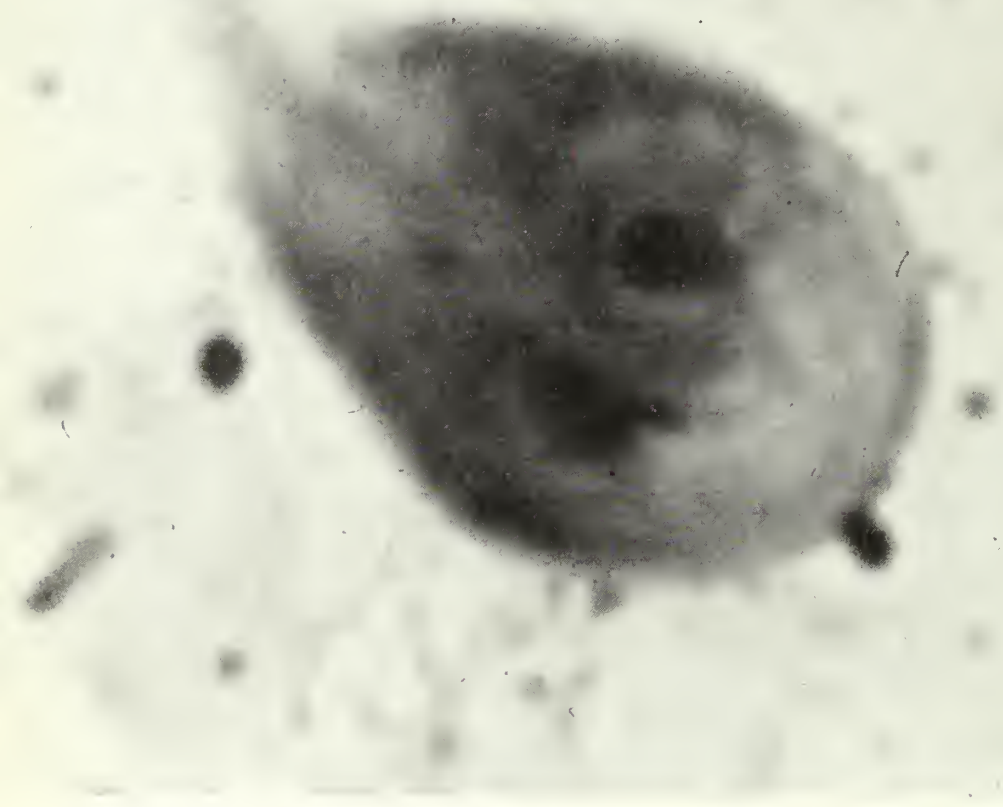
No capital investment necessary. For complete information, dial (213) 478-4275 or write:

CompuMed Systems

2139 S. Pontius Avenue · Dept. A · Los Angeles, CA 90025

GIARDIASIS.

NOW THERE IS A BETTER METHOD OF DIAGNOSIS WHEN STOOL EXAMS ARE NEGATIVE.



ENTERO-TEST,® A 140cm nylon line coiled inside of a gelatin capsule designed to retrieve duodenal contents without intubation. Easily administered and tolerated.

ENTERO-TEST® has the following advantages:

- A viable alternative to intubation
- Well tolerated by all age groups
- Pediatric sizes available
- Useful in the diagnosis of bleeding and a variety of intestinal parasites

Rosenthal and Leibman studied 23 pediatric patients with diarrhea. All had one or more negative stools. Of these, 5 patients had *Giardia lamblia* which was diagnosed by the simple ENTERO-TEST® procedure. Lopez and co-workers diagnosed Giardiasis in 22 patients with the ENTERO-TEST® compared to 4 patients by stool exams. ENTERO-TEST® has proved to be a useful and effective method for the localization of upper GI bleeding, and the diagnosis of Typhoid carriers, strongyloidiasis and other parasitic diseases.

References:

Rosenthal, P., and Liebman, W.M: Comparative study of stool examinations, duodenal aspiration, and pediatric Entero-Test for giardiasis in children. *J. PEDIAT. 96:* 278 (Feb.) 1980.

Thomas, G. E., et al: Use of the Entero-Test duodenal capsule in the diagnosis of giardiasis. *South Afr. Med J. 48:* 2219, 1974.

Lopez, M. E., et al: Infeccion duodeno-yeyunal en el niño con desnutricion energetico-proteinica. *Rev. Med. Hosp. Nat. Niños 13:* 53, 1978.

Gilman, R. H: Identification of gall typhoid carriers by a string bladder device. *The Lancet:* April 14, p. 795, 1979.

ENTERO-TEST,® The Solution. Simple And Convenient.

HEDECO

(800) 227-8162

2551 Casey Ave.
Mountain View
California 94043

THE WESTERN

Journal of Medicine

VOLUME 134 • NUMBER 5 **MAY 1981**

TABLE OF CONTENTS

379 *Mesothelioma: Current Perspectives* ROY A. TAYLOR, MD, and LLOYD P. JOHNSON, MD
From the Department of Surgery, Swedish Hospital Medical Center, and the Department of Surgery, University of Washington School of Medicine, Seattle.

384 *Primary Isolation of a New Strain of the TATLOCK/Pittsburgh Pneumonia Agent* (Legionella micdadei)
ELIZABETH A. DONEGAN, MD; MARLENE M. DEAL, PhD; M. CLAIRE MELANEPHY, BS; LESTER G. CORDES III, MD; C. WAYNE MOSS, PhD; VINCENT G. PONS, MD, and GEORGE F. BROOKS, MD
From the Departments of Laboratory Medicine and Medicine, University of California, San Francisco; and the Bureau of Epidemiology and the Bureau of Laboratories, US Public Health Service, Center for Disease Control, Atlanta.

390 *Abnormal Aminopyrine Metabolism in Patients With Chronic Hepatitis*
GERSHON W. HEPNER, MD; EDWARD PIKEN, MD, and JUAN LECHAGO, MD, PhD
From the Division of Gastroenterology, Department of Medicine, and the Department of Pathology, Harbor-UCLA Medical Center, Torrance, California.

394 *Obstetric Infections* HENRY A. OSTER, MD
From the Department of Medicine, UCLA School of Medicine, Center for the Health Sciences, Los Angeles.

MEDICAL PRACTICE

405 *Fibrositis: Misnomer for a Common Rheumatic Disorder* ROBERT M. BENNETT, MD
From the Section of Rheumatology, Department of Medicine, University of Oregon Health Sciences Center, Portland.

SPECIALTY CONFERENCE

414 *Ascites*
Participants: KAREN L. LINDSAY, MD; TELFER B. REYNOLDS, MD; JOHN C. HOEFS, MD, and MIGUEL E. SANMARCO, MD
From the Divisions of Hepatology and Cardiology, University of Southern California School of Medicine, Los Angeles, and the Rancho Los Amigos Hospital, Downey, California.

MEDICAL STAFF CONFERENCE

424 *The Great Imitator, Syphilis* Chief Discussant: FAITH FITZGERALD, MD
A discussion selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from a transcription, it was prepared by Drs. David W. Martin, Jr, Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine.

IMPORTANT ADVANCES IN CLINICAL MEDICINE

Nuclear Medicine—Epitomes of Progress
Items of progress in nuclear medicine. Each item in the judgment of a panel of knowledgeable physicians has recently become reasonably firmly established, both as to scientific fact and important clinical significance.

433 *Meckel Diverticulum, Barrett Esophagus and Retained Gastric Antrum Syndrome*
CAROL S. MARCUS, MD, and W. H. BLAHD, MD

434 *Hepatobiliary Imaging by Radionuclide Scintigraphy* RAKHI RAM, MD, and NORMAN POE, MD

434 *Serum Thyroglobulin Levels: Their Use in Monitoring Thyroid Carcinoma*
MARTIN A. SCHWARTZ, MD, and W. H. BLAHD, MD

435 *Regional Cerebral Blood Flow* NORAH MILNE, MD, and KENNETH P. LYONS, MD

435 *Adrenal Scintigraphy* ALADAR KABOK, MD, and KENNETH P. LYONS, MD

436 *Radionuclide Technique for Detection of Acute Gastrointestinal Bleeding*
RAKHI RAM, MD, and NORMAN POE, MD

436 *Leukocyte Labeling With ^{111}In Oxine for Acute Inflammatory Disease*
MYRA V. DRICKMAN, MD, and JUDITH G. ROSE, MD

437 *Detection of Acute Myocardial Infarction by Pyrophosphate ^{99m}Tc Scintigraphy*
KENNETH P. LYONS, MD, and HAL OLSON, MD

EDITORIALS

438 *Violence by Handguns*

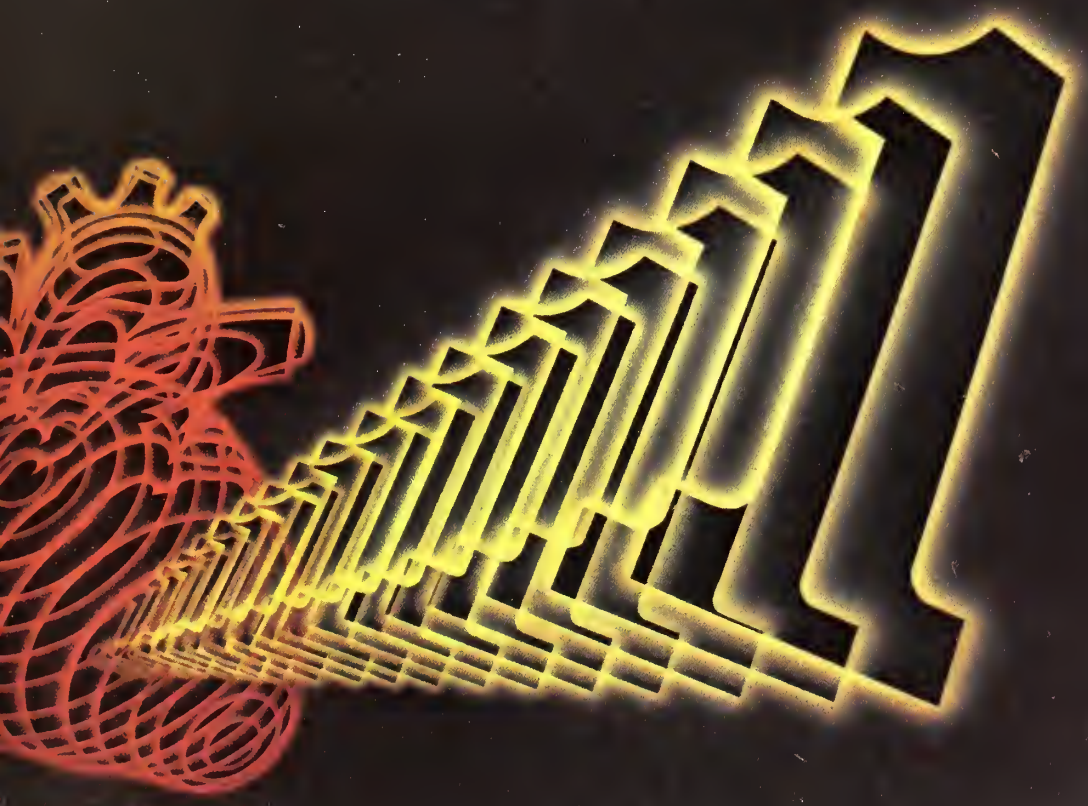
438 *Ascites* FRANK L. IBER, MD
Dr. Iber is Professor of Medicine and Chief, Gastroenterology Division, University of Maryland Hospital and the Loch Raven Veterans Administration Medical Center, Baltimore.

439 *Financial Aid for Medical Students*

(Continued on Page 11)

Only one beta-blocker provides once-a-day round-the-clock protection in both hypertension and angina pectoris.

CORGARD®
[nadolol tablets]
IS THE ONE



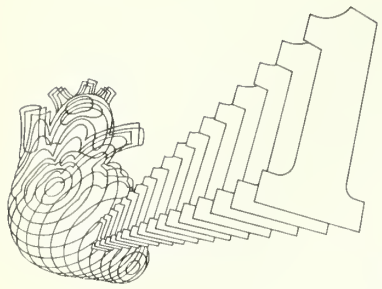
Reliable 24-hour beta blockade at all titrated dosages

SQUIBB®

Innovators in cardiovascular medicine

See next page for brief summary.

The only once-a-day beta-blocker for both hypertension and angina pectoris



CORGARD®
nadolol tablets

40 mg, 80 mg, 120 mg, 160 mg scored tablets

CORGARD® TABLETS
Nadolol Tablets

DESCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery — Because beta-blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** — Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory** — Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** — Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System** — reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal** — mesenteric arterial thrombosis; ischemic colitis. **Hematologic** — agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic** — fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous** — reversible alopecia; Peyronie's disease; erythematous rash.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm — Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval — see package insert for dosage in these patients.

For full prescribing information, consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and 1000 tablets and in Unimatic® single-dose packs of 100 tablets.

SQUIBB®

©1981 E.R. Squibb & Sons, Inc. Issued: March 1981 511-518

(Continued from Page 7)

441 *Autoerythrocyte Sensitization* WILLIAM M. BOEHME, MD, and JOHN E. KURNICK, MD
From the Divisions of Hematology, University of Colorado Medical Center, Denver, and the University of California, Irvine.

442 *Gunshot Penetrating Injuries of the Descending Thoracic Aorta*
CHARLES H. DART, Jr, MD; HOWARD E. BRAITMAN, MD, and SOMBOON LARLARB, MD
From St. John's Hospital, Oxnard, California, and the Department of Thoracic Surgery, UCLA School of Medicine, Center for the Health Sciences, Los Angeles.

446 *Lung Involvement in Progressive Vaccinia*
DAVID S. CHUDWIN, MD; MORTON J. COWAN, MD; DIANE W. WARA, MD, and ALAN C. JOHNSON, MD
From the Department of Pediatrics, University of California, San Francisco.

449 *More HAFE* EDWARD GEEHR, MD

449 *Gastrointestinal Barotrauma* KENNETH W. KIZER, MD, MPH

Alkalinization Therapy for Tricyclic Antidepressant Overdose

450 MARY LINDA H. STOTTER, PharmD

450 MICHAEL CALLAHAM, MD

451 JEROME R. HOFFMAN, MD, and CHARLES R. McELROY, MD, Reply

452 *Ascorbic Acid and Nutrition* MICHAEL S. MARGOLES, MD

452 *Hypokalemia in the Syndrome of Inappropriate Secretion of Antidiuretic Hormone*
AMIN A. NANJI, MD

453 *Medical Records as Instruments of Patient Care* GARRY S. BRODY, MD

454 *Correction: Use of Steroids in Burn Care* DAVID M. HEIMBACH, MD

Platelet Dysfunction and Migraines

454 LEE KUDROW, MD

455 LAURENCE A. HARKER, MD, Replies

Accidental Hypothermia: Hypoglycemia or Hyperglycemia

455 PHILIP ALTUS, MD, and JACK W. HICKMAN, MD

455 FAITH T. FITZGERALD, MD, Replies

456 *Appropriateness Review* ROY R. DEFFEBACH, MD

457 *Croakers' Dilemma—Should Prison Physicians Serve Prisons or Prisoners?*
KIM MARIE THORBURN, MD
Dr. Thorburn is Staff Physician, Neumiller Hospital, California State Prison at San Quentin.

462 *Announcement of the Wyoming State Medical Society Annual Meeting, Jackson, June 22-26, 1981*

463 *Fourteen Fallacies About Patient Package Inserts* JERE GOYAN, PhD
Dr. Goyan, former Commissioner of Food and Drugs, Food and Drug Administration, now is Dean of the School of Pharmacy, University of California, San Francisco.

469 *Announcement of the 89th Annual Meeting of the Idaho Medical Association, Sun Valley, July 22-25, 1981*

472 *Respiratory Physiology—Second Edition* By JOHN B. WEST, MD, PhD
Reviewed by JEFFREY A. GOLDEN, MD

472 *The Human Patient* By NAOMI REMEN, MD
Reviewed by DONALD L. FINK, MD

473 *The Courage to Fail—A Social View of Organ Transplants and Dialysis—Second Edition*
By RENEE C. FOX and JUDITH P. SWAZEY
Reviewed by H. HARRISON SADLER, MD

474 *Handbook of Obstetrics & Gynecology—7th Edition* By RALPH C. BENSON, MD
Reviewed by MORTON A. STENCHEVER, MD

474 *Annual Review of Neurosurgery—Volume 3, 1980*
By W. MAXWELL COWAN, Editor, and ZACH W. HALL and ERIC R. KANDEL, Associate Editors
Reviewed by HOWARD L. FIELDS, MD, PhD

474 *Practical Rheumatology: Diagnosis and Management* By RODNEY BLUESTONE, MB, FRCP
Reviewed by DICK L. ROBBINS, MD

475 *To Make the Patient Ready for Anesthesia: Medical Care of the Surgical Patient*
Edited by LEROY D. VANDAM, MD
Reviewed by CARTER M. BALLINGER, MD

476 *In Memoriam*

Information for Authors, See Advertising Page 26

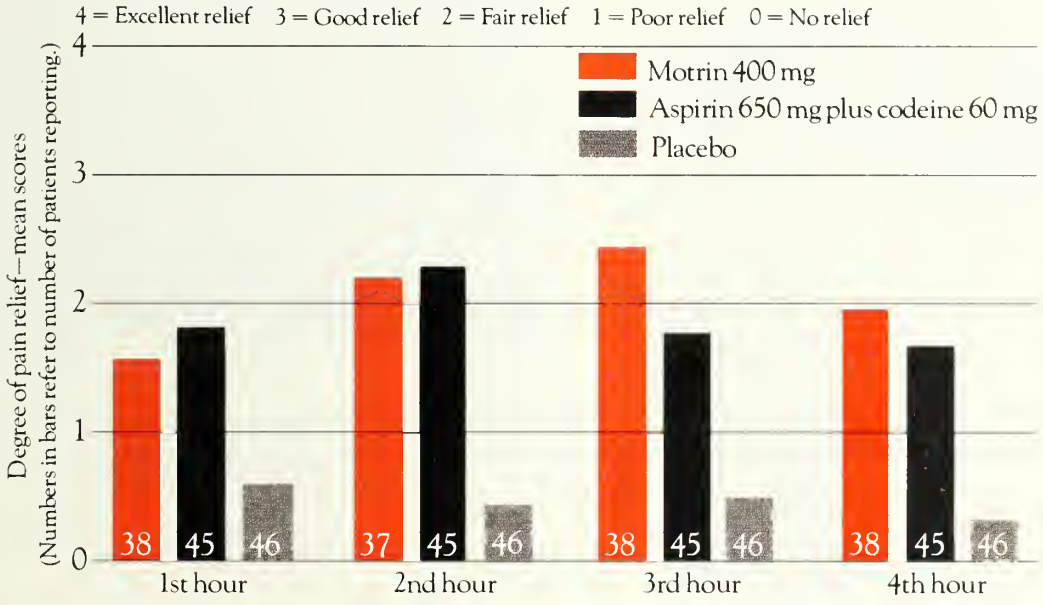
Motrin® vs aspirin w/codeine...
(ibuprofen)

©1981 The Upjohn Company

compare the analgesic effect

A *Motrin* 400 mg dose relieved postsurgical dental pain as effectively as a combination of 650 mg aspirin and 60 mg codeine (two aspirin-with-codeine No. 3 tablets) in a study of 129 patients. In this double-blind, placebo-controlled, randomized study, no statistically significant difference in relief of pain was noted at 1, 2, and 4 hours between the *Motrin* and aspirin-with-codeine groups... with *Motrin* being significantly more effective ($p = 0.03$) at the three-hour interval. Active treatment was significantly more effective ($p < 0.0001$) than placebo at all time intervals.

Comparison of pain relief
Motrin vs aspirin-codeine combination



Data on file at The Upjohn Company.

One tablet q4-6h prn
For relief of mild to moderate pain:

Motrin® 400 mg TABLETS
ibuprofen, Upjohn

• Not a narcotic • Not addictive • Not habit forming • Nonscheduled • Acts peripherally • Relieves pain rapidly • Relieves inflammation • Indicated in acute and chronic pain • Well tolerated (The most common side effect with *Motrin* is mild gastrointestinal disturbance.)

Please turn the page for a brief summary of prescribing information.

Upjohn

Motrin® (ibuprofen) now proved an effective analgesic for mild to moderate pain

Motrin® Tablets (ibuprofen, Upjohn)

Indications and Usage: Relief of mild to moderate pain.

Treatment of signs and symptoms of rheumatoid arthritis and osteoarthritis during acute flares and in long-term management. Safety and efficacy have not been established in Functional Class IV rheumatoid arthritis.

Contraindications: Individuals hypersensitive to it, or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents (see WARNINGS).

Warnings: Anaphylactoid reactions have occurred in patients with aspirin hypersensitivity (see CONTRAINDICATIONS).

Peptic ulceration and gastrointestinal bleeding, sometimes severe, have been reported. Ulceration, perforation, and bleeding may end fatally. An association has not been established. Motrin should be given under close supervision to patients with a history of upper gastrointestinal tract disease, only after consulting ADVERSE REACTIONS.

In patients with active peptic ulcer and active rheumatoid arthritis, nonulcerogenic drugs, such as gold, should be tried. If Motrin must be given, the patient should be under close supervision for signs of ulcer perforation or gastrointestinal bleeding.

Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue Motrin and the patient should have an ophthalmologic examination, including central visual fields.

Fluid retention and edema have been associated with Motrin; use with caution in patients with a history of cardiac decompensation.

Motrin can inhibit platelet aggregation and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients should report signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

To avoid exacerbation of disease or adrenal insufficiency, patients on prolonged corticosteroid therapy should have therapy tapered slowly when Motrin is added.

Drug interactions. *Aspirin:* Used concomitantly may decrease Motrin blood levels. *Coumarin:* Bleeding has been reported in patients taking Motrin and coumarin.

Pregnancy and nursing mothers: Motrin should not be taken during pregnancy nor by nursing mothers.

Adverse Reactions

Incidence greater than 1%

Gastrointestinal: The most frequent type of adverse reaction occurring with Motrin is gastrointestinal (4% to 16%). This includes nausea,* epigastric pain,* heartburn,* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of the GI tract (bloating and flatulence). **Central Nervous System:** Dizziness,* headache, nervousness. **Dermatologic:** Rash* (including maculopapular type), pruritus. **Special Senses:** Tinnitus. **Metabolic:** Decreased appetite, edema, fluid retention. Fluid retention generally responds promptly to drug discontinuation (see PRECAUTIONS).

*Incidence 3% to 9%.

Incidence less than 1 in 100

Gastrointestinal: Upper GI ulcer with bleeding and/or perforation, hemorrhage, melena. **Central Nervous System:** Depression, insomnia. **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme. **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure. **Special Senses:** Amblyopia (see PRECAUTIONS). **Hematologic:** Leukopenia, decreased hemoglobin and hematocrit.

Causal relationship unknown

Gastrointestinal: Hepatitis, jaundice, abnormal liver function. **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities. **Dermatologic:** Alopecia, Stevens-Johnson syndrome. **Special Senses:** Conjunctivitis, diplopia, optic neuritis. **Hematologic:** Hemolytic anemia, thrombocytopenia, granulocytopenia, bleeding episodes. **Allergic:** Fever, serum sickness, lupus erythematosus syndrome. **Endocrine:** Gynecomastia, hypoglycemia. **Cardiovascular:** Arrhythmias. **Renal:** Decreased creatinine clearance, polyuria, azotemia.

Overdosage: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine, so alkaline diuresis may be beneficial.

Dosage and Administration: Rheumatoid arthritis and osteoarthritis, including flares of chronic disease: Suggested dosage is 300, 400, or 600 mg t.i.d. or q.i.d. Mild to moderate pain: 400 mg every 4 to 6 hours as necessary for relief of pain.

Do not exceed 2400 mg per day.

Caution: Federal law prohibits dispensing without prescription.

For additional product information, see your Upjohn representative or consult the package insert.

Upjohn THE UPJOHN COMPANY Kalamazoo, Michigan 49001 USA

MED B-4-S

SPECIAL OFF-SEASON RATES

Maui Eldorado... The Best of Kaanapali!

A quiet hideaway at magnificent Kaanapali Beach.

A luxury lowrise resort fronted by the Royal Kaanapali Golf Course — and Kaanapali Beach! Enjoy golf, tennis, swimming in 3 pools, private beach cabana. Studios and 1 & 2 bedroom apartments. Restaurant.

SPECIAL REDUCED OFF-SEASON RATES

Effective April 1-Dec. 15, 1981

	Ocean/Golf View	Pool/Garden View
RATES:	**Nitely**	**Nitely**
Studio (1–2 pers.)	$ 58	$ 49
1 Bdrm (1–4 pers.)	$ 69	$ 79
2 Bdrm (1–6 pers.)	$139	$119

Maui Eldorado RESORT

For Reservations: Write or phone Maui Eldorado, Kaanapali, Maui, Hi 96761. Phone (808) 661-0021. **Phone Toll Free** in Continental U.S. (800) 421-0680 — In Calif. (800) 252-0078. **Or See Your Travel Agent.**

THE WESTERN Journal of Medicine

CLASSIFIED RATES

$4.00 PER LINE

(Average six words per line)

FIVE LINE MINIMUM

BOX NUMBERS $2.00 EXTRA

• • •

DISPLAY CLASSIFIED

$40 PER COLUMN INCH

Three column page rate available on request

COLUMN WIDTH

1 column 2⅛″ • 2 columns 4½″ • 3 columns 7″

(Classified Advertising is payable in advance)

Please type or print advertising copy

DEADLINE

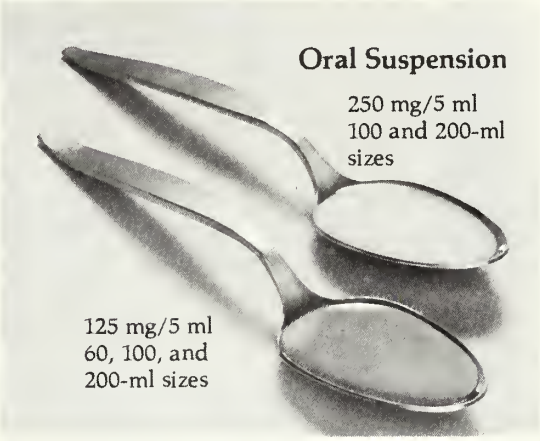
1st of Month before publication date

731 MARKET STREET

SAN FRANCISCO, CA 94103 • (415) 777-2000

easy to take

250-mg Pulvules®



Oral Suspension

250 mg/5 ml
100 and 200-ml
sizes

125 mg/5 ml
60, 100, and
200-ml sizes

Pediatric Drops

100 mg/ml
10-ml size

Keflex®
cephalexin

Additional information available
to the profession on request.

DISTA
000823

Dista Products Company
Division of Eli Lilly and Company
Indianapolis, Indiana 46285
Mfd. by Eli Lilly Industries, Inc.
Carolina, Puerto Rico 00630

DRAMATIC NEW CLINICAL PROOF*

In the treatment of impetigo–

- **100% cure rate with Tegopen®** (cloxacillin sodium)
- **only a 60% cure rate with penicillin V-K**

As seen on admission

After one week of penicillin V-K therapy

Two weeks after initiation of TEGOPEN therapy

Treatment failure was judged to have occurred when lesions increased in size and/or number during the initial week of treatment with penicillin V-K. *No* treatment failures occurred with Tegopen.

*Data on file, Bristol Laboratories.

Brief Summary of Prescribing Information

TEGOPEN®
(cloxacillin sodium)
Capsules and Oral Solution

For complete information, consult Official Package Circular (12) 9/11/75

INDICATIONS:

Although the principal indication for cloxacillin sodium is in the treatment of infections due to penicillinase-producing staphylococci, it may be used to initiate therapy in such patients in whom a staphylococcal infection is suspected. (See Important Note below.)

Bacteriologic studies to determine the causative organisms and their sensitivity to cloxacillin sodium should be performed.

IMPORTANT NOTE

When it is judged necessary that treatment be initiated before definitive culture and sensitivity results are known, the choice of cloxacillin sodium should take into consideration the fact that it has been shown to be effective only in the treatment of infections caused by pneumococci, Group A beta-hemolytic streptococci, and penicillin G-resistant and penicillin G-sensitive staphylococci. If the bacteriology report later indicates the infection is due to an organism other than a penicillin G-resistant staphylococcus sensitive to cloxacillin sodium, the physician is advised to continue therapy with a drug other than cloxacillin sodium or any other penicillinase-resistant semi-synthetic penicillin.

Recent studies have reported that the percentage of staphylococcal isolates resistant to penicillin G outside the hospital is increasing, approximating the high percentage of resistant staphylococcal isolates found in the hospital. For this reason, it is recommended that a penicillinase-resistant penicillin be used as initial therapy for any suspected staphylococcal infection until culture and sensitivity results are known.

Cloxacillin sodium is a compound that acts through a mechanism similar to that of methicillin against penicillin G-resistant staphylococci. Strains of staphylococci resistant to methicillin have existed in nature and it is known that the number of these strains reported has been increasing. Such strains of staphylococci have been capable of producing serious disease, in some instances resulting in fatality. Because of this, there is concern that widespread use of the penicillinase-resistant penicillins may result in the appearance of an increasing number of staphylococcal strains which are resistant to these penicillins.

Methicillin-resistant strains are almost always resistant to all other penicillinase-resistant penicillins (cross-resistance with cephalosporin derivatives also occurs frequently). Resistance to any penicillinase-resistant penicillin should be interpreted as evidence of clinical resistance to all, in spite of the fact that minor variations in *in vitro* sensitivity may be encountered when more than one penicillinase-resistant penicillin is tested against the same strain of staphylococcus.

CONTRAINDICATIONS:

A history of a previous hypersensitivity reaction to any of the penicillins is a contraindication.

RESULTS OF ORAL THERAPY revealed a high percentage of treatment failures with penicillin V potassium, but *no* failures with Tegopen.

		Given Tegopen® *(cloxacillin sodium)*	Given *penicillin V-K*
Staphylococcus aureus	(78 patients)	39	39
Returned to clinic at one week		29†	38†
Treatment failure at one week		0	18 (47.4%)
Staphylococcus aureus and *Streptococcus pyogenes*	(9 patients)	4	5
Returned to clinic at one week		4	5
Treatment failure at one week		0	2 (40%)
No initial bacterial growth	(14 patients)	9	5
All 14 healed, regardless of which antibiotic was administered.			
Beta-hemolytic *Streptococcus*	(1 patient)	0	1
TOTALS:	**102 patients**	**52 patients**	**50 patients**

†Eleven patients did not return for their one-week checkup. These were all called by telephone, and their families reported the lesions had healed. One patient was dropped from the study, early, because of adverse reaction to medication.

STUDY: DESCRIPTION/PROTOCOL

- 102 nonselected subjects, with initial bacteriology as follows: 77% *Staphylococcus aureus*, 9% mixed *Staphylococcus aureus* and *Streptococcus pyogenes*, and 1% beta-hemolytic *Streptococcus*.‡
- All patients were given randomized therapy—Tegopen capsules or oral solution, or penicillin V-K tablets or oral solution, in recommended dosages according to body weight.
- All patients were evaluated after one week's therapy. If there was no improvement, therapy was switched to the other antibiotic. The "other antibiotic" proved to be Tegopen 100% of the time because no treatment failures had occurred with Tegopen.
- A final assessment of progress was made two weeks after initiation of Tegopen therapy.

‡The remainder, to equal 100%, consisted of 14 patients (13%) who exhibited no initial bacterial growth. These 14 were all healed, whether given Tegopen or penicillin V-K.

TEGOPEN®
(cloxacillin sodium)
–effective therapy for staph infections of the skin and skin structures

WARNING:
Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents, e.g., pressor amines, antihistamines, and corticosteroids.

Safety for use in pregnancy has not been established.

PRECAUTIONS:
The possibility of the occurrence of superinfections with mycotic organisms or other pathogens should be kept in mind when using this compound, as with other antibiotics. If superinfection occurs during therapy, appropriate measures should be taken.

As with any potent drug, periodic assessment of organ system function, including renal, hepatic, and hematopoietic, should be made during long-term therapy.

ADVERSE REACTIONS:
Gastrointestinal disturbances, such as nausea, epigastric discomfort, flatulence, and loose stools, have been noted by some patients. Mildly elevated SGOT levels (less than 100 units) have been reported in a few patients for whom pretherapeutic determinations were not made. Skin rashes and allergic symptoms, including wheezing and sneezing, have occasionally been encountered. Eosinophilia, with or without overt allergic manifestations, has been noted in some patients during therapy.

USUAL DOSAGE:
Adults: 250 mg. q 6h.

Children: 50 mg./Kg./day in equally divided doses q 6h. Children weighing more than 20 Kg should be given the adult dose. Administer on empty stomach for maximum absorption.

N B INFECTIONS CAUSED BY GROUP A BETA-HEMOLYTIC STREPTOCOCCI SHOULD BE TREATED FOR AT LEAST 10 DAYS TO HELP PREVENT THE OCCURRENCE OF ACUTE RHEUMATIC FEVER OR ACUTE GLOMERULONEPHRITIS.

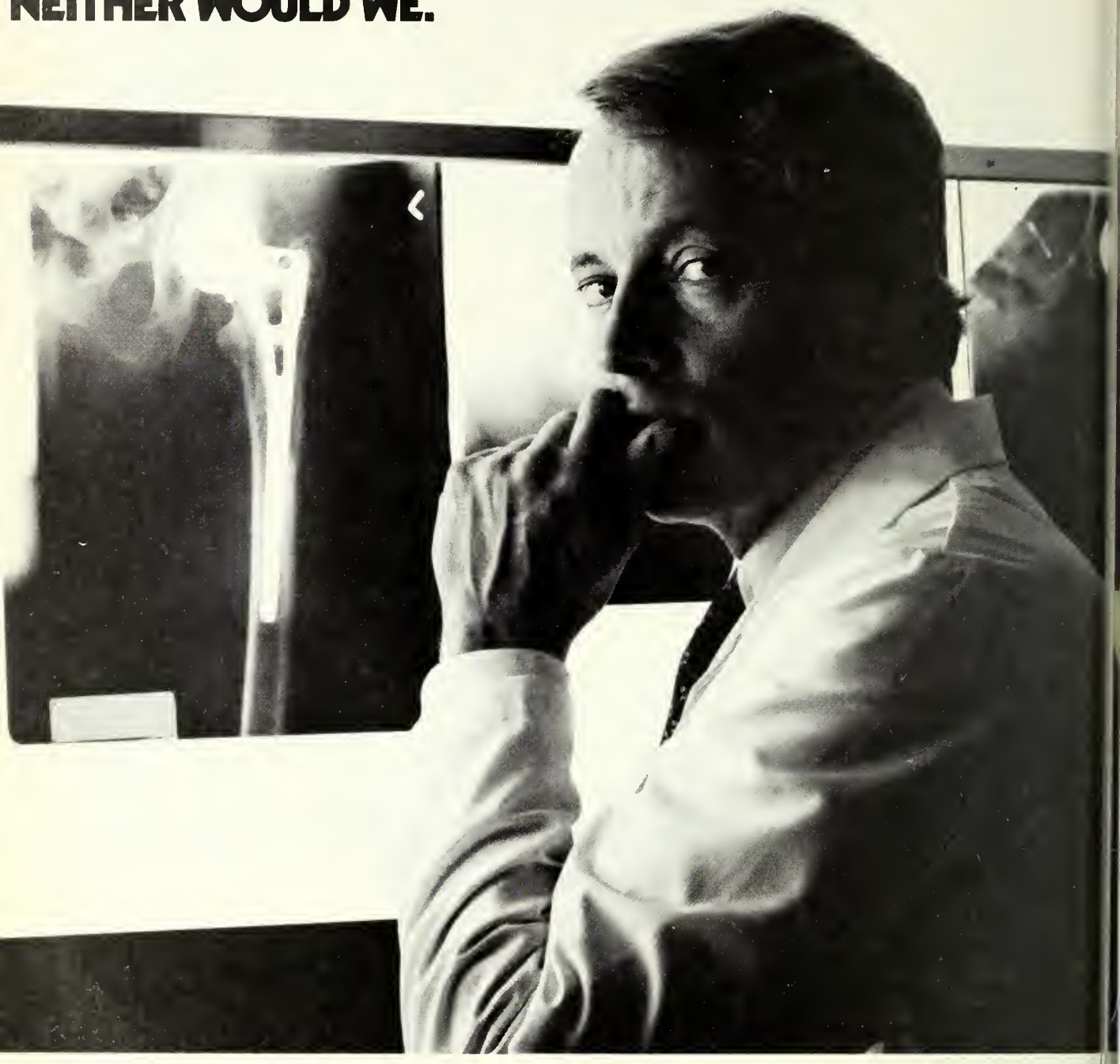
SUPPLIED:
Capsules—250 mg. in bottles of 100, 500 mg. in bottles of 100.
Oral Solution—125 mg./5 ml. in 100 ml. and 200 ml. bottles.

BRISTOL®
Bristol Laboratories
Division of Bristol-Myers Company
Syracuse, New York 13201

Copyright © 1981, Bristol Laboratories

WOULD YOU GUARANTEE THERE WON'T BE PROBLEMS OVER THE NEXT 5 YEARS?

NEITHER WOULD WE.



Responsible physicians know that despite sound medical judgment and specialized skills, their prognoses are often subject to uncertainty.

You must make allowances for potential adversity and you should expect your professional liability insurance company to do the same.

Responsible medical malpractice insurers, like The Doctors' Company, know that their policyholders' long-range interests are best protected by financial strength and solvency. That's why we maintain the largest surplus of all the doctor-owned malpractice insurers in the western United States. That's why our earned premium to surplus ratio is the most favorable of all these companies. And that's why we continue to collect surplus contributions from new members.

Future results can't be guaranteed, in the fragile art of medicine or in the volatile business of malpractice insurance. Our allowance for adversity is surplus.

For details about our program, call or write: The Doctors' Compa 233 Wilshire Blvd., Santa Monica, CA 90401. (213) 451-9936. Toll free, (800) 352-7271. Outside California, (800) 421-2368.

THE DOCTORS' COMPAN

AN INTERINSURANCE EXCHANGE
OFFERING MEDICAL MALPRACTICE INSURANC
TO DOCTORS IN
CALIFORNIA, NEVADA, WYOMING AND MONTAN

CONTINUING MEDICAL EDUCATION

California, Hawaii, Nevada; Alaska, Montana, Idaho; New Mexico; Oregon; Washington; Utah

CALIFORNIA, HAWAII and NEVADA

This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000, ext. 146. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

June 4-7—**California Society of Anesthesiologists—Annual Scientific Meeting.** Hyatt Regency, San Francisco. Thursday-Sunday. 20 hrs. $100, members; $200, nonmembers. Contact: CSA, 100 E. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

August 4-11—**A Clinical Update on Anesthesia Practice.** California Society of Anesthesiologists Alaskan Cruise aboard the Island Princess. One week. 21 hrs. $250, CSA members; $350, nonmembers. Contact: Richard Manley, CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

August 23-26—**Clinical Neuroanesthesia.** California Society of Anesthesiologists at UCSD. Sunday-Wednesday. 24 hrs. $325, CSA members; $375, nonmembers. Contact: Richard Manley, CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

August 29-30—**Hemodynamic Monitoring—Pulmonary Artery Catheterization.** See "Of Interest to All," August 29-30.

September 12-13—**Weekend Seminar.** Calif. Society of Anesthesiologists at Sahara Hotel, Lake Tahoe. Saturday-Sunday. Contact: CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

CANCER

May 18-22—**Medical Oncology Review.** American College of Physicians at University of Hawaii School of Medicine, Honolulu. Monday-Friday. Contact: Postgraduate Dept., ACP, 4200 Pine St., Philadelphia, PA 19104. (215) 243-1200.

June 10—**Carcinomas of the Uterus and Ovaries.** LLU. Wednesday. 4 hrs. $30.

June 13-17—**Head and Neck Oncology.** UCLA. Saturday-Wednesday.

EMERGENCY MEDICINE

May 25-26—**Advanced Cardiac Life Support.** Emergency Care Education Center at Queen Mary, Long Beach. Monday-Tuesday. 12 hrs. $130. Contact: ECEC, P.O. Box 9639, Marina Del Rey 90291. (213) 822-1312.

May 26-30—**California Chapter, American College of Emergency Physicians—10th Annual Scientific Assembly.** Jack Tar Hotel, San Francisco. Tuesday-Saturday. Contact: Calif. Chap., ACEP, 6839 Lincoln Blvd., Suite 240, Los Angeles 90045.

May 28-30—**3rd Annual Trauma Seminar.** DREW at Disneyland Hotel, Anaheim. Thursday-Saturday. Contact: S. Balasubramaniam, MD, Div. of Emergency Medicine, Charles R. Drew Postgraduate Medical School, 1621 E. 120th St., Los Angeles 90059. (213) 603-5235.

June 6—**Management of Trauma and Its Complications.** See Surgery, June 6.

June 10-December 9—**Emergency Medicine.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Second Wednesday of each month; 7:30-9:00 p.m. Contact: Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-2311.

June 15-19—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $425.

June 26-27—**Orthopedics in Emergency Medicine—An In-Depth Review.** UCLA at Miramar-Sheraton Hotel, Santa Monica. Friday-Saturday. 14 hrs. $180.

June 29-July 3—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

July 24-26—**Advanced Cardiac Life Support Workshops.** Emergency Medical Systems at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact. EMS, 2310 Mason St., San Francisco 94133. (415) 956-5900.

July 27-28—**Advanced Cardiac Life Support.** Emergency Care Education Center at Queen Mary, Long Beach. Monday-

(Continued on Page 23)

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center 2801 Atlantic Ave., Long Beach 90801. (213) 595-3837.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

When she can't manage, you can.

The sweats. The hot flushes. The distress and discomfort of atrophic vaginitis. The possibility of osteoporosis.* The menopause.

For many women, it's a time of confusion and frustration. Counseling can help her overcome these feelings. But counseling *can't* stop vasomotor and vaginal symptoms, or retard bone loss*...the true signs of estrogen deficiency. And that's where she needs you most.

You're an expert at estrogen replacement. You know why it should be used. When it's best avoided. How to cycle therapy. Determine dosage. Check for contraindications and possible complications. Follow-up. You know when therapy should begin, and when it deserves to end.

Most of all, you know your patient—and when she needs the effective relief you can give her with PREMARIN.

When it comes to managing the estrogen-deficiency symptoms of the menopause, you've got what it takes.

*Conjugated Estrogens Tablets have been evaluated as probably effective for postmenopausal osteoporosis

Prescribed with care by physicians who care.

PREMARIN®
BRAND OF
CONJUGATED ESTROGENS TABLETS, U.S.P.
0.3 mg/0.625 mg/1.25 mg/2.5 mg

Please see following page for brief summary of prescribing information.

BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION, SEE PACKAGE CIRCULAR)

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA

Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year[1-3] This risk was independent of the other known risk factors for endometrial cancer These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade[4] The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4 5 to 13 9 times greater than in nonusers. The risk appears to depend on both duration of treatment[1] and on estrogen dose[3] In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration,[3] it therefore appears prudent to utilize such a regimen Close clinical surveillance of all women taking estrogens is important In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY

The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare[5,6] This risk has been estimated as not greater than 4 per 1000 exposures[7] Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis,[8-12] epithelial changes of the vagina and cervix Although these changes are histologically benign, it is not known whether they are precursors of malignancy Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects[13-16] One case control study[16] estimated a 4 7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion) Some of these exposures were very short and involved only a few days of treatment The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000 In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation

DESCRIPTION: PREMARIN (Conjugated Estrogens Tablets, U.S.P.) for oral administration contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications for use as follows

Effective:

1 Moderate to severe *vasomotor* symptoms associated with the menopause (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions)

2 Atrophic vaginitis.

3 Kraurosis vulvae

4 Female hypogonadism

5 Female castration

6 Primary ovarian failure

7 Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease

8 Prostatic carcinoma—palliative therapy of advanced disease

9 Postpartum breast engorgement—Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens[19]

PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING)

"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures Final classification of this indication requires further investigation

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions 1 Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease 2 Known or suspected estrogen-dependent neoplasia 3 Known or suspected pregnancy (See Boxed Warning) 4 Undiagnosed abnormal genital bleeding 5 Active thrombophlebitis or thromboembolic disorders 6 A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy)

WARNINGS: At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast,[17] although a recent study has raised this possibility[18] There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens[17]

Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement, it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement[19-22] Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction[23-30] Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users[31,32] An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives[33,34] If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization Estrogens should not be used in persons with active thrombophlebitis, thromboembolic disorders, or in persons with a history of such disorders in association with estrogen use They should be used with caution in patients with cerebral vascular or coronary artery disease Large doses (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown[35] to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. When doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a clear risk

Benign hepatic adenomas should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives[36] Increased blood pressure may occur with use of estrogens in the menopause[37] and blood pressure should be monitored with estrogen use A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives For this reason, diabetic patients should be carefully observed Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed Conditions influenced by fluid retention such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc Oral contraceptives appear to be associated with an increased incidence of mental depression[23a] Patients with a history of depression should be carefully observed Preexisting uterine leiomyomata may increase in size during estrogen use The pathologist should be advised of estrogen therapy when relevant specimens are submitted If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated Estrogens should be used with care in patients with impaired liver function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete.

The following changes may be expected with larger doses of estrogen

a Increased sulfobromophthalein retention

b Increased prothrombin and factors VII, VIII, IX, and X, decreased antithrombin 3, increased norepinephrine-induced platelet aggregability

c Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered

d Impaired glucose tolerance

e Decreased pregnanediol excretion

f Reduced response to metyrapone test

g Reduced serum folate concentration

h Increased serum triglyceride and phospholipid concentration

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhea, premenstrual-like syndrome, amenorrhea during and after treatment, increase in size of uterine fibromyomata, vaginal candidiasis, change in cervical erosion and in degree of cervical secretion, cystitis-like syndrome, tenderness, enlargement, secretion (of breasts), nausea, vomiting, abdominal cramps, bloating, cholestatic jaundice, chloasma or melasma which may persist when drug is discontinued, erythema multiforme, erythema nodosum, hemorrhagic eruption, loss of scalp hair, hirsutism; steepening of corneal curvature, intolerance to contact lenses, headache, migraine, dizziness, mental depression, chorea, increase or decrease in weight, reduced carbohydrate tolerance, aggravation of porphyria, edema, changes in libido.

ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females

DOSAGE AND ADMINISTRATION: 1 *Given cyclically for short term use only* For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0 3 to 1 25 mg or more daily)

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible

Administration should be cyclic (e g three weeks on and one week off)

Attempts to discontinue or taper medication should be made at three to six month intervals

2 *Given cyclically* Female hypogonadism Female castration Primary ovarian failure Osteoporosis

Female hypogonadism—2 5 to 7 5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration. If bleeding does not occur by the end of this period, the same dosage schedule is repeated The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium

If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U.S.P.), 2 5 to 7 5 mg daily in divided doses, for 20 days During the last five days of estrogen therapy, give an oral progestin If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding

Female castration and primary ovarian failure—1 25 mg daily, cyclically Adjust upward or downward according to response of the patient For maintenance, adjust dosage to lowest level that will provide effective control

Osteoporosis (to retard progression)—1 25 mg daily, cyclically

3 *Given for a few days* Prevention of postpartum breast engorgement—3 75 mg every four hours for five doses, or 1 25 mg every four hours for five days

4 *Given chronically* Inoperable progressing prostatic cancer—1 25 to 2 5 mg three times daily

Inoperable progressing breast cancer in appropriately selected men and postmenopausal women—10 mg three times daily for a period of at least three months

Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding

HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U.S.P.) No 865—Each *purple* tablet contains 2 5 mg in bottles of 100 and 1,000 No 866—Each *yellow* tablet contains 1.25 mg in bottles of 100 and 1,000 Also in unit dose package of 100 No 867—Each *red* tablet contains 0 625 mg in bottles of 100 and 1,000 Also in unit dose package of 100 No 868—Each *green* tablet contains 0 3 mg in bottles of 100 and 1,000

PHYSICIAN REFERENCES: 1 Ziel, H K, *et al* N Engl J Med *293*:1167-1170, 1975 2 Smith, D C, *et al*: N Engl J Med *293*:1164-1167, 1975 3 Mack, T M, *et al*: N Engl J Med *294*:1262-1267, 1976 4 Weiss, N S, *et al*: N Engl J Med *294*:1259-1262, 1976 5 Herbst, A L, *et al*: N Engl J Med *284*:878-881, 1971 6 Greenwald, P, *et al*: N Engl J Med *285*:390-392, 1971 7 Lanier, A, *et al*, Mayo Clin Proc *48*:793-799, 1973 8 Herbst, A, *et al*: Obstet Gynecol *40*:287-298, 1972 9 Herbst, A, *et al*: Am J Obstet Gynecol. *118*:607-615, 1974 10 Herbst, A, *et al* N Engl J Med *292*:334-339, 1975 11 Stafl, A, *et al*: Obstet Gynecol. *43*:118-128, 1974 12 Sherman, A I, *et al* Obstet Gynecol *44*:531-545, 1974 13 Gal, I, *et al* Nature *216*:83, 1967 14 Levy, E P, *et al*: Lancet *1*:611, 1973 15 Nora, J, *et al* Lancet *1*:941-942, 1973 16 Janerich, D T, *et al*: N Engl J Med *291*:697-700, 1974 17 Boston Collaborative Drug Surveillance Program N Engl J Med *290*:15-19, 1974 18 Hoover, R, *et al*: N Engl J Med *295*:401-405, 1976 19 Daniel, D G, *et al*: Lancet *2*:287-289, 1967 20 The Veterans Administration Cooperative Urological Research Group J Urol. *98*:516-522, 1967 21 Bailar, J C Lancet *2*:560, 1967 22 Blackard, C, *et al*: Cancer *26*:249-256, 1970 23 Royal College of General Practitioners: J R Coll Gen Pract *13*:267-279, 1967. 23a Royal College of General Practitioners Oral Contraceptives and Health, New York, Pitman Corp, 1974 24 Inman, W H W, *et al*: Br Med J *2*:193-199, 1968 25 Vessey, M P, *et al*: Br Med J *2*:651-657, 1969 26 Sartwell, P E, *et al*: Am J Epidemiol *90*:365-380, 1969 27 Collaborative Group for the Study of Stroke in Young Women: N Engl J Med *288*:871-878, 1973 28 Collaborative Group for the Study of Stroke in Young Women J A M A *231*:718-722, 1975 29 Mann, J I, *et al*: Br Med J *2*:245-248, 1975 30 Mann, J I, *et al*: Br Med J *2*:241-245, 1975 31 Inman, W H W, *et al*: Br Med J *2*:203-209, 1970 32 Stolley, P D, *et al* Am J Epidemiol *102*:197-208, 1975 33 Vessey, M P, *et al*: Br Med J *3*:123-126, 1970 34 Greene, G R, *et al* Am J Public Health *62*:680-685, 1972 35 Coronary Drug Project Research Group J A M A *214*:1303-1313, 1970 36 Mays, E T, *et al*: J A M A *235*:730-732, 1976 37 Pfeffer, R I, *et al* Am J Epidemiol *103*:445-456, 1976

7457/181

Ayerst® AYERST LABORATORIES
New York, N.Y. 10017

(Continued from Page 19)

Tuesday. 12 hrs. $130. Contact: ECEC, P.O. Box 9639, Marina Del Rey 90291. (213) 822-1312.

August 3-7—**Postgraduate Institute for Emergency Room Physicians, Symposium II.** UCSD. Monday-Friday. 40 hrs. $425.

September 14-18—**Postgraduate Institute for Emergency Room Physicians, Symposium I.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $425.

September 28-29—**Advanced Cardiac Life Support.** Emergency Care Education Center at Queen Mary, Long Beach. Monday-Tuesday. 12 hrs. $130. Contact: ECEC, P.O. Box 9639, Marina Del Rey 90291. (213) 822-1312.

October 2-3—**Symposium on Medical Emergencies.** UCLA at Miramar-Sheraton Hotel, Santa Monica. Friday-Saturday. 14 hrs. $180.

October 19-23—**Postgraduate Institute for Emergency Room Physicians, Symposium III.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $425.

MEDICINE

May 18-21—**Endocrinology for the Practicing Physician.** LLU at Mauna Kea Beach Hotel, Kamuela, Hawaii. Monday-Thursday. 16 hrs. $200.

May 18-22—**Advances in Internal Medicine.** UCSF at Hyatt on Union Square, San Francisco. Monday-Friday.

May 23-30—**Allergy and Immunology.** Univ. of Washington School of Medicine at Wailea Beach, Maui, Hawaii. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle 98195.

May 31-June 4—**Internal Medicine for the Generalist—1981.** UCSD at Hilton, San Diego. Sunday-Thursday. 23 hrs.

June 1-5—**Advances in Internal Medicine.** UCSF. Monday-Friday.

June 3—**Gastroenterology.** St. Francis Medical Center, Lynwood. Wednesday. 6 hrs. Contact: Allan M. Hoffman, EdD, Dir. of Med. Ed., St. Francis Med. Ctr., 3630 Imperial Highway, Lynwood 90262. (213) 603-6174.

June 12—**Current Concepts in Cardiac Rehabiliation.** American Heart Assn., Greater Los Angeles Affiliate, at Hilton Hotel, Los Angeles. Friday. 6 hrs. $75, AHA member; $90, nonmember. Contact: Ben Jacobowitz, AHA, Greater LA Affiliate, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231, ext. 55.

June 12-14—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Sahara Hotel, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

June 26-28—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Sheraton, Anaheim. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

July 10-11—**Frontiers in Cardiology.** San Diego Heart Institute, Alvarado Community Hospital, at Hyatt Islandia Hotel, San Diego. Friday-Saturday. Contact: Allan L. Simon, MD, San Diego Heart Institute, Alvarado Community Hosp., 6655 Alvarado Rd., San Diego 92120. (714) 287-3270.

July 11-18—**Endocrine Metabolic Course.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 25 hrs. $350.

July 13-17—**Third International Psoriasis Symposium.** STAN. Monday-Friday.

July 18-25—**Cardiovascular Medicine and Surgery: An Advanced Course.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 23 hrs. $295.

August 7-8—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Doubletree Inn, Monterey. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

August 12-15—**Workshop in Medical Mycology/Dermatomycology.** Memorial Hospital Medical Center-UCI Center for Health Education at Newporter Inn, Newport Beach. Wednesday-Saturday. Contact: Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

August 15-21—**Neuropsychiatric Issues in the Law, Education and Medicine: Hyperactivity and Dyscontrol Syndrome.** See Psychiatry, August 15-21.

August 21-22—**Cardiac Rehabilitation.** International Medical Education Corp. at Sheraton, Anaheim. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

September 5-9—**Dermatopathology.** UCD at Silverado Country Club, Napa. Saturday-Wednesday.

September 18-20—**Cardiac Ischemia and Arrhythmias—Current Concepts for Diagnosis and Treatment.** International Medical Education Corp. at Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

September 25—**Hypertension.** UCD. Friday.

September 25-26—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Holiday Inn, San Francisco. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112, (800) 525-8646.

October 3—**4th Annual Heart Symposium.** Northridge Hospital at Century Plaza Hotel, Los Angeles. Saturday. Contact: Dept. of Med. Ed., Northridge Hospital, 18300 Roscoe Blvd., Northridge 91328. (213) 885-8500.

October 9-11—**California Society of Internal Medicine—Annual Meeting.** Marriott's Rancho Las Palmas Resort, Rancho Mirage. Friday-Sunday. Contact: Carol Parlette, Exec. Dir., CSIM, 703 Market St., Suite 1412, San Francisco 94103.

October 12-16—**An Advanced Course for Internists.** STAN. Monday-Friday. 25 hrs.

October 14—**Thrombophlebitis and Thromboembolic Disease.** LLU. Wednesday. 4 hrs.

October 16-17—**Advances in Internal Medicine.** So. Calif. Permanente Medical Group at Century Plaza Hotel, Los Angeles. Friday-Saturday. Contact: Shirley Gach, Education and Research, SCPMG, 4747 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

October 16-18—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Sahara Hotel, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

October 18-22—**Pacific Dermatologic Association—Annual Meeting.** Reno. Monday-Thursday. Contact: Florence Beardsley, Exec. Sec., PDA, 180 Mark Twain Ave., Reno 89509. (702) 323-2461.

October 25-29—**American College of Chest Physicians.** Hilton Hotel, San Francisco. Sunday-Thursday. 30 hrs. Contact: Dept. of Education, ACCP, 911 Busse Highway, Park Ridge, IL 60068. (312) 698-2200.

OBSTETRICS AND GYNECOLOGY

June 10—**Carcinomas of the Uterus and Ovaries.** See Cancer, June 10.

(Continued on Page 39)

Classified Advertisements

The rate for each insertion is **4.00 per line** (average six words per line) **with five line minimum.**

Box number charge: $2.00 each month.

Classified display rates $40.00 per inch.

Copy for classified advertisements should be received not later than **the fifth of the month preceding issue. All copy must be typed or printed.** • Classified advertisers using Box Numbers forbid the disclosure of their identity. Your inquiries in writing will be forwarded to Box Number advertisers. The right is reserved to reject or modify all classified advertising copy in conformity with the rules of the Advertising Committee.

Please Type or Print Advertising Copy

CLASSIFIED ADVERTISEMENTS ARE PAYABLE IN ADVANCE

PHYSICIANS WANTED

INDUSTRIAL PHYSICIAN—In the heart of the Rockies. National Company seeking MD or DO with emphasis in general or internal medicine. Prefer Board Certified in Occupational Medicine. Responsibilities will include employee physicals, routine and emergency treatment of injuries and providing assistance in health maintenance and education program for Company employees. Forty-hour work week with generous benefits and compensation package. Excellent outdoor recreation opportunities abundantly available. Send CV to: Employment (WJM-MN), EG&G Idaho, Inc., P.O. Box 1625, Idaho Falls, ID 83415. Equal Opportunity Employer M/F/H/V. U.S. citizenship required.

PHYSICIANS WANTED

WYOMING: Emergency Medicine—Summer locum tenens for experienced emergency physicians in busy resort hospital located in Jackson, Wyoming. Average of 56 hours per week with flexible scheduling arrangement. Must be available June 5 through September 14 inclusive, without exception. Excellent hourly compensation plus paid professional liability insurance. For further information, contact William Salmo at 1-(800)-525-3681 (in Colorado call collect (303) 471-4981).

STUDENT HEALTH PHYSICIAN—San Jose State University 12 hours per week/10 month position, $1,316/month. Specializing in orthopedic medicine. Must be Board certified orthopedist by California Board of Medical Quality Assurance. Send résumé to R. C. Miller, MD, Director, Student Health Service, San Jose State University, San Jose, CA 95192.

LAS VEGAS, NEVADA: Emergency Medicine Opportunity-Clinical position available in this modern facility south of Las Vegas. Flexible scheduling according to individual needs allows time to enjoy the numerous recreational facilities in the surrounding countryside. Minimum guarantee plus paid professional liability insurance. For details send credentials in confidence to William Salmo, Chase Stone Center, Holly Sugar Building, Suite 1070, Colorado Springs, CO 80903 or call toll-free 1 (800) 525-3681 (within Colorado, call collect (303) 471-4981).

COLORADO EMERGENCY MEDICINE: Directorship and Clinical positions available in Northeastern portion of the state in moderate volume emergency department. Hourly quarantee plus compensation for Director's added responsibilities. Paid professional liability insurance and other amenities. For further information contact William Salmo toll-free 1 (800) 525-3681 (within Colorado call collect (303) 471-4981); or send credentials in confidence to Chase Stone Center, Holly Sugar Building, Suite 1070, Colorado Springs, CO 80903.

PHYSICIANS WANTED

PHYSICIAN WANTED: Green Valley, Arizona, satellite clinic looking for Board Certified or Board Eligible Family Practitioner to join one other Family Practitioner. Minimum 5 years experience preferred. Office practice only. Excellent income and fringe benefits. Reply to Box 6189, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

OPPORTUNITY FOR A BOARD CERTIFIED/QUALIFIED INTERNIST in San Diego area. Retiring physician with two younger associates in expense-sharing group desires replacement to assume existing practice in growing area. Gerald W. Ondash, MD, 105 Durian St., Vista, CA 92083. Telephone (714) 726-5722.

CALIFORNIA: Faculty member for Family Practice Residency Program located in Orange County. Prefer Residency trained, Board Certified Family Physician. Practice and/or teaching experience preferred. Responsibilities include In-Patient coordination of Residency Program or Out-Patient teaching activities. Salary negotiable. Program affiliated with University of Southern California, School of Medicine. Send all inquiries and CV to: Raymond Jones, MD, Chairman, Search Committee, 1200 North Tustin Ave., Suite 260, Santa Ana, CA 92705. Phone: (714) 547-5404.

WESTERN ARIZONA AND SOUTHERN NEVADA —EMERGENCY MEDICINE: Clinical and Directorship positions available in several emergency departments. Excellent compensation, paid professional liability insurance, flexible scheduling. For further details contact William Salmo toll-free at 1 (800) 525-3681 (within Colorado call collect (303) 471-4981); or send credentials in complete confidence to Chase Stone Center, Holly Sugar Building, Suite 1070, Colorado Springs, CO 80903.

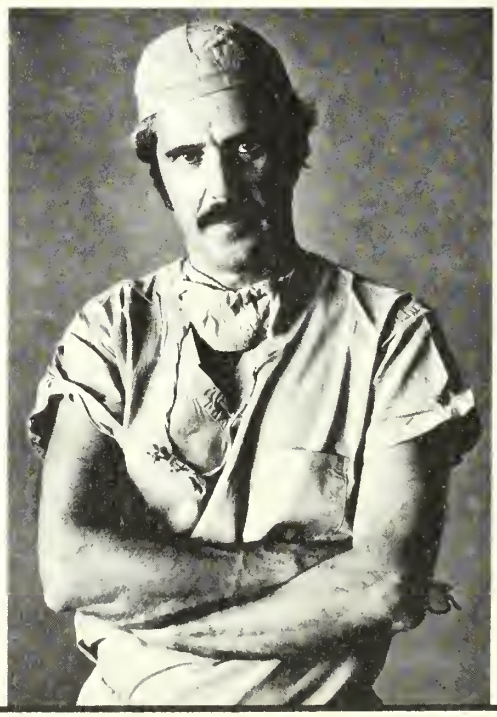
(Continued on Page 34)

We've taken the pain out of establishing your practice.

As a physician you're familiar with ways to alleviate pain. But chances are, your extensive educational process has not prepared you to handle the problems of selecting a location and establishing a successful private practice. National Medical Enterprises' Professional Relations Department has a staff of highly trained people who can help take the anguish out of making this important decision.

If you are familiar with NME you know us as one of America's largest and fastest growing health care companies that owns, operates, and manages acute care facilities that meet or exceed JCAH standards.

NME can provide Board Eligible/Board Certified physicians with private practice opportunities from Seattle, Washington to St. Petersburg, Florida - opportunities that enable you to concentrate on medicine while we assist you through the start-up phase of your new practice.



NME can offer you some of the best equipped health care facilities in the nation along with modern offices, a diverse choice of climates and a community ideally suited to your lifestyle.

Let us take the pain out of establishing a practice for you. Write and send us your curriculum vitae. Let us know your interests and where you want to live and practice. For additional information, contact:

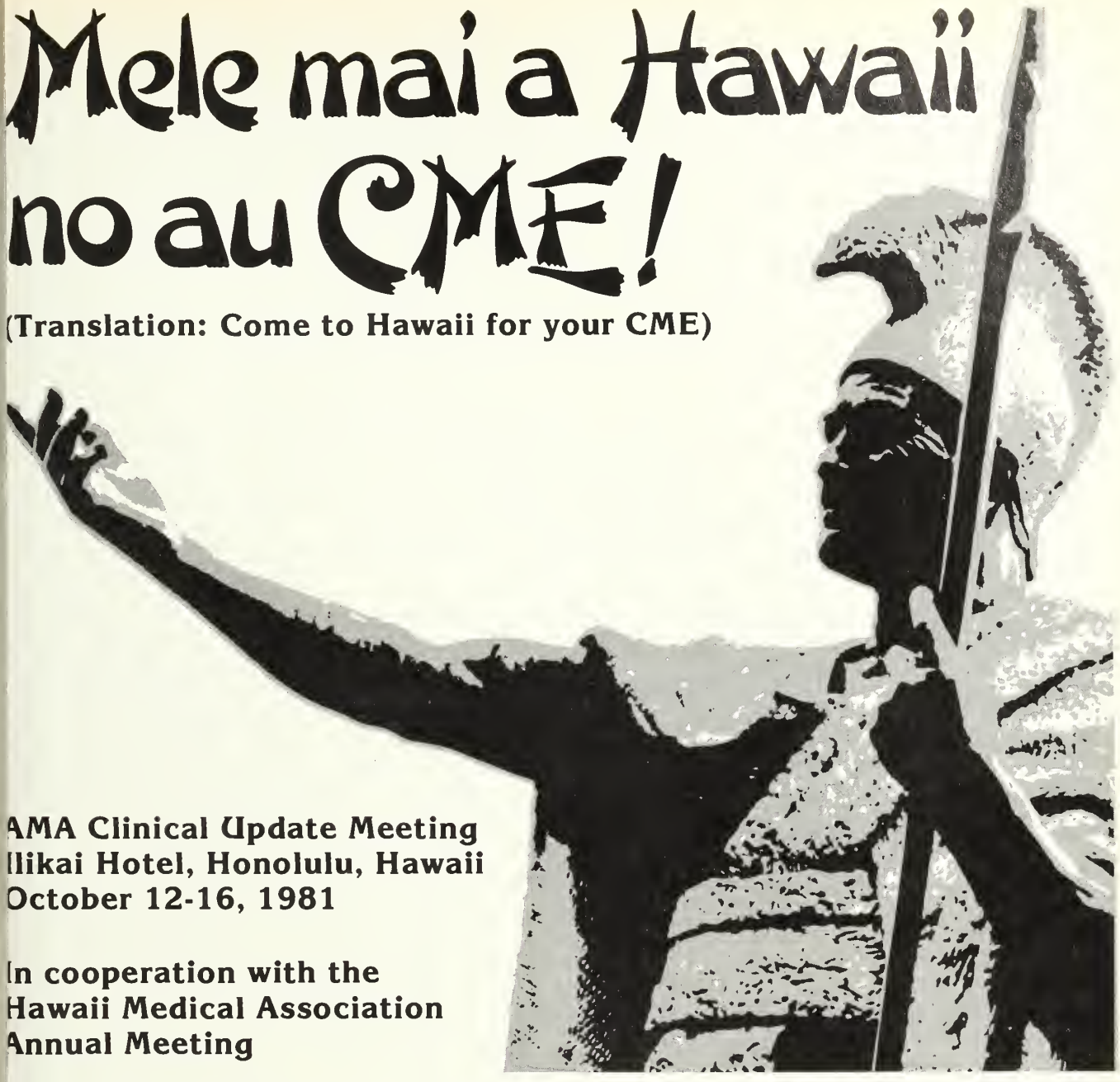
Raymond C. Pruitt
Director, Physician Relations
National Medical Enterprises
11620 Wilshire Blvd.
Los Angeles, California 90025
(213) 479-5526
1-800-421-7470

nme NATIONAL MEDICAL ENTERPRISES, INC.

"The total health care company."

Mele mai a Hawaii no au CME!

(Translation: Come to Hawaii for your CME)



AMA Clinical Update Meeting
Ilikai Hotel, Honolulu, Hawaii
October 12-16, 1981

In cooperation with the Hawaii Medical Association Annual Meeting

Thirty 5-hour Postgraduate Courses, Monday-Friday
Choose from 30 Category 1 courses in such specialty areas as cardiology, internal medicine, family medicine, general surgery, pharmacology, pediatrics and gynecology. Substantial syllabi accompany these courses.

Post Meeting Tour to Maui!
Three nights, four days (Saturday-Tuesday, October 17-20) at the Intercontinental Hotel on beautiful, unspoiled Maui. To save on the inter-island portion of the trip, buy your ticket from continental cities to Honolulu and Maui.

Buy Your Plane Tickets Early!
Air fares are increasing rapidly, so obtain your tickets early to get the lowest possible fare.

Plan NOW for Your Trip to Hawaii!
You can surf, golf, go sight-seeing and deep-sea fishing or just relax and let the sun and gentle Tradewinds work their wonders.

Return this coupon for complete information!

Department of Meeting Services
American Medical Association
535 North Dearborn Street WJ
Chicago, Illinois 60610

Please send me information on the AMA Update Meeting in Hawaii, October 12-16, 1981.

Please Print

Name _____

Address _____

City/State/Zip _____

THE WESTERN JOURNAL OF MEDICINE
INFORMATION FOR AUTHORS

Submitting Manuscripts

Manuscripts for consideration should be sent to the editor, Malcolm S. M. Watts, MD, 731 Market Street, San Francisco, California 94103. The transmittal letter should designate one person as correspondent and include complete address, with ZIP code and telephone number.

In view of *The Copyright Revision Act of 1976*, transmittal letters should contain the following language: "In consideration for reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns or otherwise conveys all copyright ownership to THE WESTERN JOURNAL OF MEDICINE in the event that such work is published by the journal." This statement should be signed by *all* the authors.

Authors are urged to seek clarity and succinctness in all manuscripts regardless of subject matter or format, and to give close attention to syntax, grammar and spelling.

Preparing Manuscripts

The original manuscript and *two* copies should be submitted on heavy bond paper (8½ by 11 inches, *not* erasable), typed double-spaced throughout (including legends, tables and references) on one side of the paper, with 1½-inch margins. Ordinarily, articles should not exceed 3,000 words (less than 15 text pages, typed double-spaced). Under exceptional circumstances only will articles longer than 4,000 words be published. Pages should be numbered consecutively, beginning with the title page.

Style

Abbreviations. Use of abbreviations should be minimized. If they are necessary, abbreviations should be spelled out at first mention, with the abbreviation itself immediately following in parentheses.

Weights and measures. All measurements should be given in metric units. English equivalents should be given parenthetically if the measurements were originally done in English units.

Temperatures. Temperature readings should be given first in Celsius, followed by the Fahrenheit equivalent in parentheses.

Drug names. If the trade name of a drug is used, the generic name should be given first, followed by the trade name in parentheses. Trade names are capitalized, generic names are not.

Title Page

Titles are best when brief and concise. The title page should include the full name of the author(s), with degrees, academic or professional titles, complete addresses and any institutional or other affiliations. The complete name and address of the person who will handle reprint requests also should appear on this page.

Abstract

The abstract (approximately 150 words) should be a short summary, saying in brief what is said at length in the body of the article—rather than such and such "is discussed," "is presented" or "was investigated."

Tables and Figures

Tables

Each table should be typed on a separate sheet of paper, be numbered consecutively in Arabic numerals, have a brief descriptive title and have its position indicated in the text.

Illustrations (Figures)

Three sets of clear, unmounted black and white glossy prints of figures should be submitted (preferably 5 by 7 inches, but no larger than 8½ by 11 inches). For line drawings, original artwork or glossy prints are acceptable. Illustrations should be numbered consecutively in Arabic numerals and their position indicated in the text. Figure number, first author's name and top of the photo should be shown on the reverse side of each illustration. Recognizable photographs of patients are to be masked and written permission for publication obtained from the patients.

Legends

All legends for figures should be typed together on a separate sheet of paper. Magnification and stain for photomicrographs should be indicated in parentheses.

Permission for Reproduction

If an illustration or table has been used previously in another publication, written permission for its use must be obtained from the publisher, and should accompany the manuscript. The source should be acknowledged in the legend if it can be done briefly by citation of a reference number. Otherwise, acknowledgment is made at the end of the figure legend or at the bottom of the table.

References

References should be limited to those cited in the text. They must be typed double-spaced and numbered consecutively as they appear in the manuscript. (See examples below for style.) Abbreviations of journal titles should conform to those used in *Index Medicus.*

Journal Articles

Note handling of multiple authorship. If more than three authors are listed as contributors, use "et al" to designate those names after the first three. Also note capitalization, punctuation, mention of inclusive page numbers, and month and year of publication. Separate the subtitle from the title by either a dash or a colon. Use colon *only* if it appears in the original citation.

1. Jones JS, Anderson HW, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 292:444-456, Apr 26, 1978

2. Graybill JR, Alford RH, Smith RG, et al: Cell-mediated immunity in cryptococcosis: A brief review. Cell Immunol 7: 76-79, Sep 1978

Books

Note handling of "edition," "editor(s)," and "volume," as well as appropriate sequence of reference information and capitalization of chapters and titles.

3. Berne EJ, Smith TL: Role playing in therapy, chap 2, Principles of Group Therapy. New York, Oxford University Press, 1966, pp 35-51 *(author of chapter same as author of book)*

4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, IL, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

Pamphlets, Monographs or Books With No Given Author

5. AMA Department of Drugs: AMA Drug Evaluation, 3rd Ed. Littleton, MA, Publishing Sciences Group, Inc, 1977 *(corporate author)*

6. Compilation of Standard Definitions, 3rd Ed. Philadelphia. American Society for Testing and Materials, 1976 *(no given author; give name and place of publisher)*

Articles in Press or Accepted for Publication

Any article accepted for publication should include the name of the journal (appropriately abbreviated) in which it will appear, and the phrase "in press" or "accepted for publication" in place of the date of publication.

Personal Communications and Unpublished Data

This information should *not* be included in the reference list but should be given in parentheses within the body of the text. Date of communication, whether it was personal or written, and the person's name, highest academic degree and professional affiliation should be provided.

Acknowledgments

It is the policy of the *WJM* not to print acknowledgments, the feeling being that if a person has contributed enough to a paper to be mentioned, he or she should be included among the authors, or the contribution should be mentioned in the body of the paper or in a footnote.

Correspondence

Brief manuscripts commenting on articles that have appeared in the journal, containing information of interest to physicians or discussing issues of the day will be considered for publication. Very short reports of cases, clinical experience, clinical studies, adverse effects and the like also will be considered. Items for the Correspondence section should not exceed 600 words and should have no more than five bibliographic references and one figure or table.

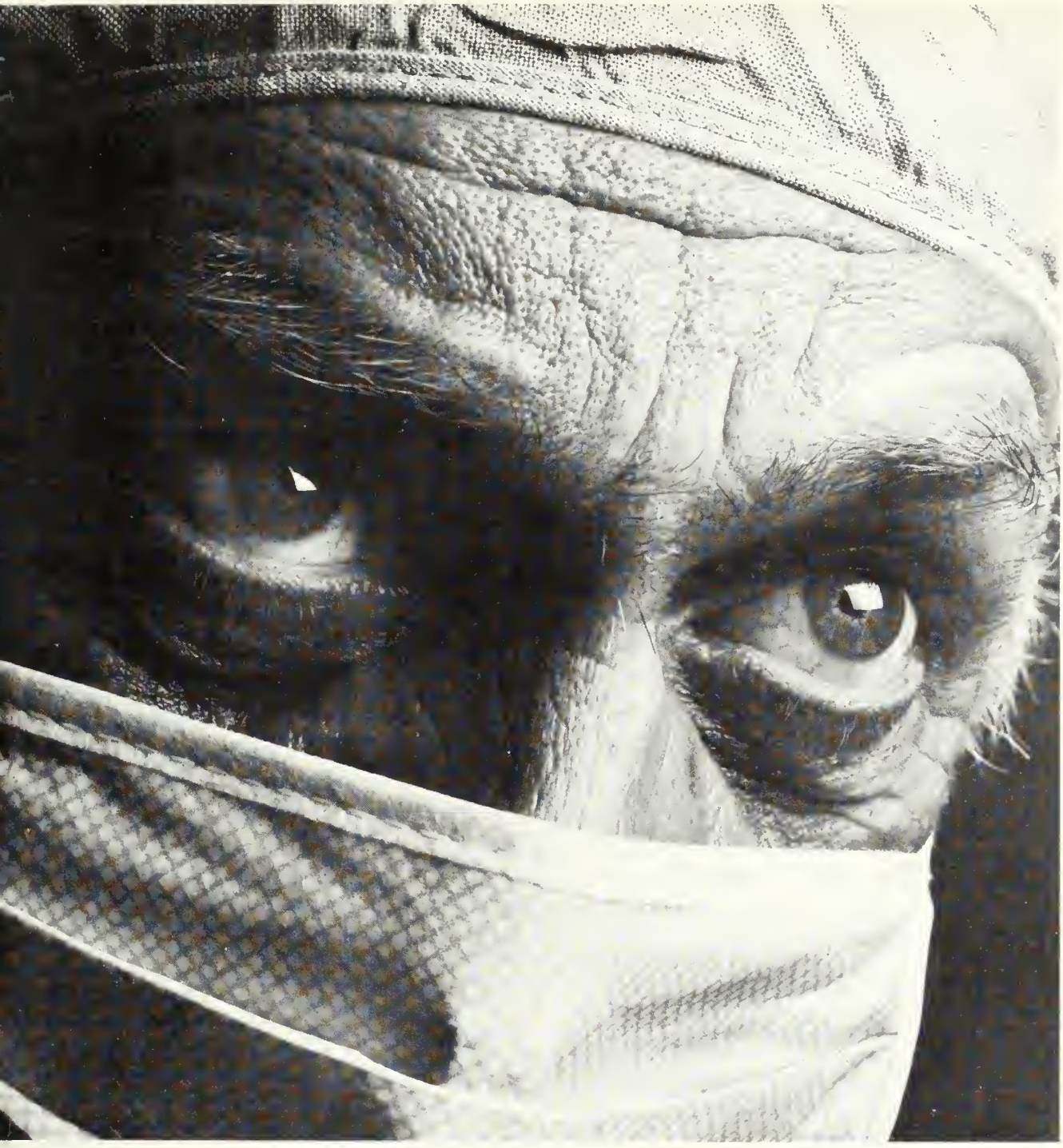
Author Responsibility

Authors are responsible for all statements made in articles. Manuscripts are considered for publication with the explicit understanding that they are original, have not been published previously and are not simultaneously under consideration by any other publication.

All accepted manuscripts are subject to copy editing, and authors are sent edited galleys for approval. No changes will be made after the final, edited version has been approved by the author.

Reprints

If reprints are desired, they must be paid for by the author. A reprint order form with schedule of prices is sent to the author when the article is published. Authors are responsible for handling requests for reprints of their articles.



Commitment.

It is evident in a doctor's every action. Commitment. It is the key to professional excellence. In the medical field. And in ours.

At Insurance Corporation of America our commitment has always been to a single goal: To provide physicians with the finest professional liability insurance.

Over the years ICA has consistently offered the strongest possible coverage combined with the highest standard of professional service. Our specialization, conservative management, and commitment in this one field have enabled us to achieve excellence within the industry.

For further information, contact: Insurance Corporation of America, ICA Center 4295 San Felipe, Box 56308, Houston, Texas 77027. 1-800-231-2615. In Texas call 1-800-392-9702 (Check for availability in your state.)

ICA **PROFESSIONAL LIABILITY INSURANCE.**

WE'RE THE SPECIALIST IN THE FIELD.

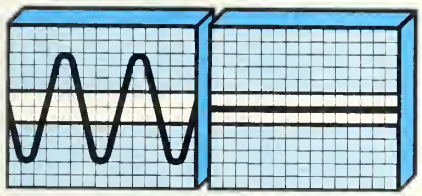
$\frac{dc}{dt} = K$

We straightened out the problem of theophylline blood levels.

THEO-DUR® (anhydrous theophylline)– The first and only form of oral theophylline to demonstrate linear blood levels for a full 12 hours.

The problem with theophylline blood levels is that they are difficult to maintain in the therapeutic range and difficult to sustain for more than a few hours.

For most patients, the therapeutic range of theophylline is somewhere between 10 and 20 mcg/ml. If serum concentrations fall much below 10, theophylline is often ineffective. If they go much above 20, they are usually toxic.



Other oral theophyllines produce blood levels that float in and out of the therapeutic range

THEO-DUR produces linear blood levels that remain therapeutic

THEO-DUR is the only form of oral theophylline to offer linear serum concentrations. It minimizes the peak-trough fluctuations common to many other oral theophyllines. Once titrated, linear serum concentrations assure that THEO-DUR will remain therapeutic.

And, since THEO-DUR maintains therapeutic blood levels for 12 hours, patients can enjoy a full day of normal activities and a night of uninterrupted sleep.

Zero-order THEO-DUR–a unique form of oral theophylline.

THEO-DUR produces linear serum concentrations because THEO-DUR has zero-order absorption. The drug is absorbed into the blood at a constant quantity per hour.

Other oral forms of theophylline have first-order absorption, in which the largest amount is absorbed in the first hour and proportionately smaller amounts thereafter.

When absorption varies, as it does with first-order drugs, protection can also vary. That's why first-order theophyllines can be toxic within the first few hours and subtherapeutic later on.

THEO-DUR–the practical benefits.

Your patient benefits from the maximum control provided by THEO-DUR in several important ways: exercise tolerance is increased, emergency hospital visits are less likely and concomitant therapy is usually unnecessary.

Dosage titration is easy to achieve* THEO-DUR is the only sustained-action tablet in 200 mg as well as 100 and 300 mg strengths, and all tablets are scored for greater dosage flexibility.

THEO-DUR also enhances patient compliance–with an every 12 hour dosage schedule that's easier to remember.

**After three days, on a steady dose, serum concentrations should be monitored and appropriate dosage adjustments made, if necessary.*

THEO-DUR®
anhydrous theophylline
Sustained Action Tablets

Today's most widely-prescribed bronchodilator.

KEY PHARMACEUTICALS, INC.

Please see next page for a summary of prescribing information

THEO-DUR®

anhydrous theophylline

Sustained Action Tablets

300 mg 200 mg 100 mg

The first and only form of oral theophylline to demonstrate linear blood levels for a full 12 hours.

Description: THEO-DUR Sustained Action Tablets contain anhydrous theophylline, with no color additives

Pharmacologic Actions: The pharmacologic actions of theophylline are as a bronchodilator, pulmonary vasodilator and smooth muscle relaxant since the drug directly relaxes the smooth muscle of the bronchial airways and pulmonary blood vessels. Theophylline also possesses other actions typical of the xanthine derivatives: coronary vasodilator, diuretic, cardiac stimulant, cerebral stimulant and skeletal muscle stimulant. The actions of theophylline may be mediated through inhibition of phosphodiesterase and a resultant increase in intracellular cyclic AMP which could mediate smooth muscle relaxation.

Indications and Usage: Symptomatic relief and/or prevention of asthma and reversible bronchospasm associated with chronic bronchitis and emphysema.

Contraindications: THEO-DUR is contraindicated in individuals who have shown hypersensitivity to any of its components or xanthine derivatives.

Warnings: Excessive theophylline doses may be associated with toxicity; serum theophylline levels should be monitored to assure maximum benefit with minimum risk. Incidence of toxicity increases at serum levels greater than 20 mcg/ml. High blood levels of theophylline resulting from conventional doses are correlated with clinical manifestation of toxicity in: patients with lowered body plasma clearances, patients with liver dysfunction or chronic obstructive lung disease, and patients who are older than 55 years of age, particularly males. There are often no early signs of less serious theophylline toxicity such as nausea and restlessness, which may appear in up to 50% of patients prior to onset of convulsions. Ventricular arrhythmias or seizures may be the first signs of toxicity. Many patients who have higher theophylline serum levels exhibit a tachycardia. Theophylline products may worsen pre-existing arrhythmias.

Usage in Pregnancy: Safe use in pregnancy has not been established relative to possible adverse effects on fetal development, but neither have adverse effects on fetal development been established. This is, unfortunately, true for most anti-asthmatic medications. Therefore, use of theophylline in pregnant women should be balanced against the risk of uncontrolled asthma.

Precautions: THEO-DUR TABLETS SHOULD NOT BE CHEWED OR CRUSHED. Theophyllines should not be administered concurrently with other xanthine medications. It should be used with caution in patients with severe cardiac disease, severe hypoxemia, hypertension, hyperthyroidism, acute myocardial injury, cor pulmonale, congestive heart failure, liver disease, and in the elderly, particularly males, and in neonates. Great caution should be used in giving theophylline to patients in congestive heart failure since these patients show markedly prolonged theophylline blood level curves. Use theophylline cautiously in patients with history of peptic ulcer. Theophylline may occasionally act as a local irritant to G.I. tract, although gastrointestinal symptoms are more commonly central and associated with high serum concentrations above 20 mcg/ml.

Adverse Reactions: The most consistent adverse reactions are usually due to overdose and are:

Gastrointestinal: Nausea, vomiting, epigastric pain, hematemesis, diarrhea.

Central Nervous System: Headaches, irritability, restlessness, insomnia, reflex hyperexcitability, muscle twitching, clonic and tonic generalized convulsions.

Cardiovascular: Palpitation, tachycardia, extrasystoles, flushing, hypotension, circulatory failure, life threatening ventricular arrhythmias.

Respiratory: Tachypnea.

Renal: Albuminuria, increased excretion of renal tubular cells and red blood cells, potentiation of diuresis.

Others: Hyperglycemia and inappropriate ADH syndrome.

How Supplied: THEO-DUR 100 mg, 200 mg and 300 mg Sustained Action Tablets are available in bottles of 100, 1000, and 5000, and in unit dose packages of 100.

Caution: FEDERAL LAW PROHIBITS DISPENSING WITHOUT A PRESCRIPTION.

For full prescribing information, see package insert.

0281

KEY PHARMACEUTICALS, INC.
50 N.W. 176th Street
Miami, Florida 33169

TD-1137

KF®

DIABETES and the KIDNEY

14th Annual Symposium
ON
RENAL DISEASE

SPONSORED BY THE

NATIONAL KIDNEY FOUNDATION
of Northern California

Friday, September 18
San Francisco Hilton Hotel
San Francisco, CA

Subjects and faculty are:

- **Diabetes—Prevalence, Genetics and Classification,**
  Dr. Clinton Young, San Francisco
- **Diabetic Vascular Diseases,**
  Dr. Marvin Siperstein, San Francisco
- **Diabetic Nephropathy, Morphology and Functional Correlates of Progression,**
  Dr. Bryan Myers, Stanford
- **Renal Retinal Syndrome,**
  Dr. Eli Friedman, New York
- **Treatment of Diabetic Retinopathy,**
  Dr. John Cavender, San Francisco
- **Is Diabetic Nephropathy Preventable?**
  Dr. Eli Friedman
- **Artificial Pancreas,**
  Dr. Clinton Young
- **Renal Transplant in the Diabetic,**
  Dr. John Najarian, Minneapolis
- **Pancreatic Transplant in the Diabetic,**
  Dr. Roy Calne, Cambridge, England.

Symposium Director:
DR. BARRY LEVIN, Presbyterian Hospital, San Francisco
Tuition: Physicians $60, Allied Health Professionals, $25

This course is acceptable for 9 hours Category I Credit towards the CMA. Continuing education credit pending for Allied Health Professionals.

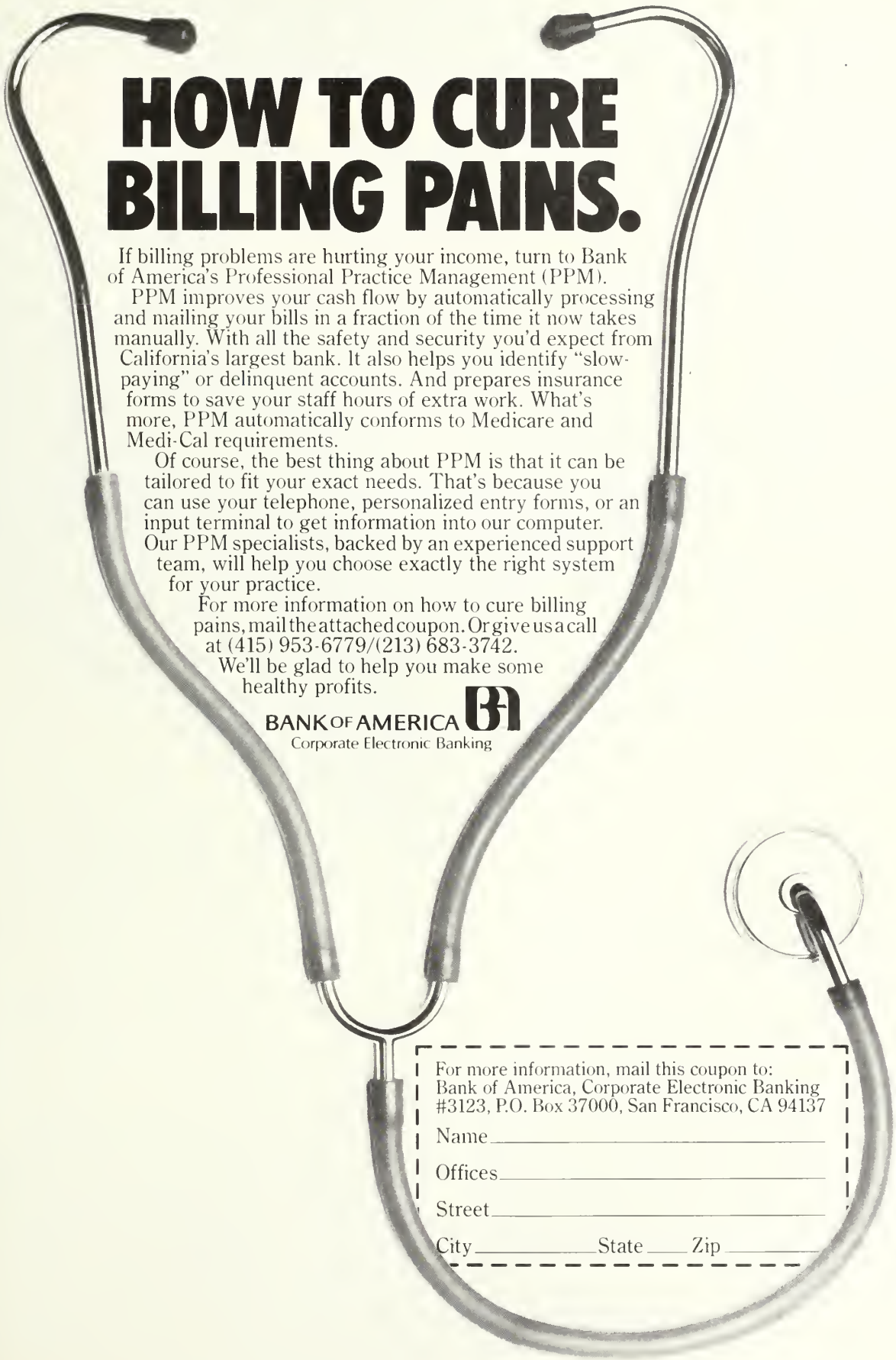
For further Information and Registration contact:
National Kidney Foundation of Northern California
856 Stanton Road
Burlingame, CA 94010
(415) 697-0110

CLASSIFIED

INFORMATION

(415) 777-2000

EX 220



HOW TO CURE BILLING PAINS.

If billing problems are hurting your income, turn to Bank of America's Professional Practice Management (PPM).

PPM improves your cash flow by automatically processing and mailing your bills in a fraction of the time it now takes manually. With all the safety and security you'd expect from California's largest bank. It also helps you identify "slow-paying" or delinquent accounts. And prepares insurance forms to save your staff hours of extra work. What's more, PPM automatically conforms to Medicare and Medi-Cal requirements.

Of course, the best thing about PPM is that it can be tailored to fit your exact needs. That's because you can use your telephone, personalized entry forms, or an input terminal to get information into our computer. Our PPM specialists, backed by an experienced support team, will help you choose exactly the right system for your practice.

For more information on how to cure billing pains, mail the attached coupon. Or give us a call at (415) 953-6779/(213) 683-3742. We'll be glad to help you make some healthy profits.

BANK OF AMERICA
Corporate Electronic Banking

For more information, mail this coupon to:
Bank of America, Corporate Electronic Banking
#3123, P.O. Box 37000, San Francisco, CA 94137

Name _____

Offices _____

Street _____

City _____ State ____ Zip _____

Bank of America NT&SA Member FDIC

In Hypertension*...When You Need to Conserve K^+

Every Step of the Way

Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

†Step 1 usually consists of an initial phase (a diuretic alone), a titration phase (dosage adjustment and/or addition of a K^+ supplement or K^+-sparing agent), and a maintenance phase (a diuretic alone or in combination with a K^+ supplement or K^+-sparing agent).

Serum K^+ and BUN should be checked periodically (see Warnings).

Before prescribing, see complete prescribing information in SK&F Co. literature or *PDR*. The following is a brief summary.

* **WARNING**

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K^+ frequently: both can cause K^+ retention and elevated serum K^+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded; in the other, serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia, although uncommon, has been reported. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis and of impotence have been reported with the use of 'Dyazide' although a causal relationship has not been established

Supplied: Bottles of 1000 capsules, Single Unit Packages (unit-dose) of 100 (intended for institutional use only), in Patient-Pak™ unit-of-use bottles of 100.

© SK&F Co., 1980

SK&F CO.
a SmithKline company
Carolina, P.R. 00630

THE WESTERN
Journal of Medicine

Refer to: Taylor RA, Johnson LP: Mesothelioma: Current Perspectives. West J Med 134:379-383, May 1981

Mesothelioma: Current Perspectives

ROY A. TAYLOR, MD, *and* LLOYD P. JOHNSON, MD, *Seattle*

Thirty patients with the diagnosis of mesothelioma were admitted to the Swedish Hospital Medical Center, Seattle, from 1975 to 1979. Of these, 26 had pleural and 4 had peritoneal mesothelioma. In 20 of the patients with pleural mesothelioma, the diagnosis had been made by open thoractomy and in only one by needle biopsy of the pleura. The average survival of the patients with pleural tumors from time of diagnosis was 15 months, and two are alive at three and eight months, respectively, one of whom had an apparent solitary benign mesothelioma. The average survival of those with peritoneal mesothelioma was ten months, although one has survived six years. There were 17 patients with a known history of exposure to asbestos, 14 while working in shipyards. Because of the relatively high incidence of this previously rare tumor in the Puget Sound, Washington, area, and the generally dismal results of therapy, better methods of diagnosis including thoracoscopy and a more systematic approach to treatment are recommended.

In recent years, mesothelioma, a tumor of serosal surfaces, has become a subject of growing interest among the medical profession and the lay public. The attention is due both to its increasing frequency of diagnosis and its strong epidemiological link to asbestos exposure.[1-7] Asbestos, a mineral fiber, is valued for its thermal properties and has found wide application in this century as an insulating material. Until recently, including the busy years of World War II, it was used extensively in ship building as pipe insulation. Growing evidence indicates that the populations in those areas with ship building activities have a significantly increased risk of developing mesothelioma.[1,8] In a tumor registry study by Hinds[8] of eight areas of the United States, the Puget Sound area and New Orleans, both with substantial shipyard activity, had the highest incidence of mesothelioma. During the past 4½ years, one registry reported 85 cases of malignant pleural mesothelioma in western Washington (written communication, June 1980, Fred Hutchinson Cancer Research Center, Seattle).

Because of this somewhat unusual epidemiology, the apparent increasing incidence of the disease and the generally poor results of therapy, we wish to review our recent experience with mesothelioma and propose some new directions for its diagnosis and management.

Clinical Presentation

The cases of 30 patients admitted to the Swedish Hospital Medical Center in Seattle between 1975 and 1979 were reviewed. In all of the patients mesothelioma had been diagnosed by tissue analysis. There were 25 with diffuse malignant pleural disease, 4 with peritoneal tumor and 1

From the Department of Surgery, the Swedish Hospital Medical Center, Seattle (Dr. Taylor), and the Department of Surgery, University of Washington School of Medicine, Seattle (Dr. Johnson).

Submitted September 29, 1980.

Reprint requests to: Lloyd P. Johnson, MD, Seattle Surgical Group, Inc., P.S., 801 Broadway, Suite 901, Seattle, WA 98122.

with a benign localized pleural mesothelioma (Table 1).

Peritoneal Mesothelioma

Three of the four patients with peritoneal mesothelioma were men. The average age at diagnosis was 59 years. Two patients had a known history of exposure to asbestos, one of these had worked in shipyards 25 years earlier. The most common symptoms were abdominal pain, loss of weight, abdominal distension and fever. Three of the patients had ascites and in one of these a gallium scan and abdominal ultrasound examination showed abnormalities. Paracentesis was carried out in two but was diagnostic in neither. Laparotomy was required for diagnosis in all four patients. The tumor was described as being diffuse with matting of the bowel in three patients. One patient had metastasis to the liver, lung and sealene nodes. Two of the patients died two weeks after diagnosis and a third died after nine months.

Of interest, the fourth patient was a woman who had a predominant pelvic tumor with involvement of the colon and uterus as well as omental nodules. She was treated by resection of the tumor, followed by radiation and chemotherapy. She is still alive six years after the time of diagnosis, and there is no evidence of recurring disease.

Benign Pleural Mesothelioma

In the one patient with benign localized pleural mesothelioma, an asymptomatic mass of the left side was detected on an x-ray study of the chest. Over five years the lesion increased in size from 2 to 8 cm (see Figure 1). She had no history of asbestos exposure. During thoracotomy a solitary benign mesothelioma was found and was removed without difficulty. The patient is doing well six months following resection, and there is no evidence of recurrent tumor.

Malignant Pleural Mesothelioma

Twenty of 25 patients with diffuse pleural mesothelioma were men. The average age at diagnosis was 61 years. Fifteen patients had a known exposure to asbestos, 13 of them in shipyards. The average interval from time of exposure to diagnosis was 32 years.

The clinical presentation of these cases is given in Table 1. The most common symptoms were chest pain and dyspnea. Pleural effusion was

TABLE 1.—*Clinical Symptoms of 25 Patients With Diffuse Pleural Disease**

	No. of Patients
Symptoms	
Dyspnea	11
Chest pain	9
Weakness	7
Fever	7
Findings on roentgenograms	
Pleural effusion	20
Pleural nodularity	11

*In one other patient with pleural mesothelioma, the condition was diagnosed as a solitary benign tumor.

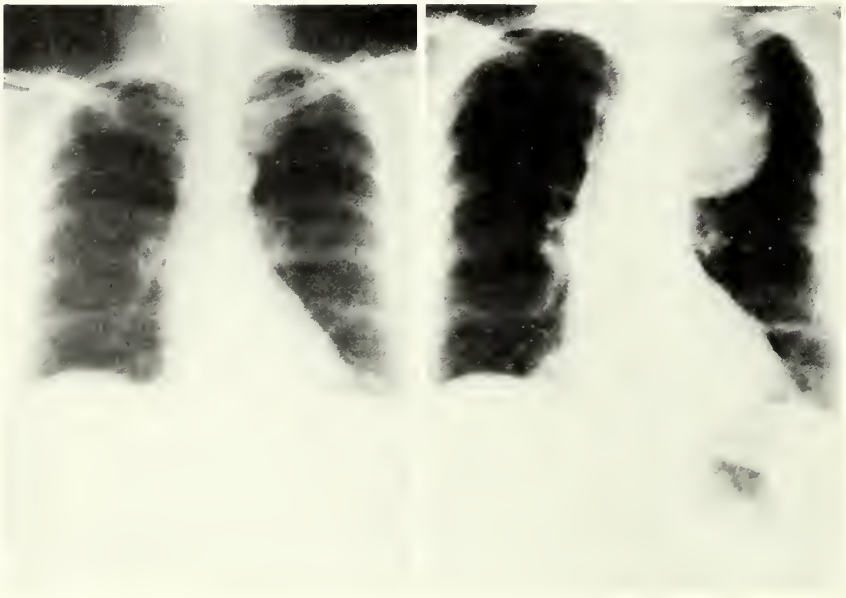


Figure 1.—X-ray studies of the chest showing growth of a benign pleural mesothelioma from 2 to 8 cm over five years.

present in 20 of 25 patients. The common findings on chest roentgenograms, as represented in Figure 2, included pleural effusion, pleural nodules—demonstrated best by pneumothorax—and pleural plaques, which were calcified and probably benign.

Diagnostic procedures are listed in Table 2. In 19 patients a diagnosis was made by thoracotomy. Cytologic studies of pleural fluid and needle biopsies of the pleura have not been productive. Recently, thoracoscopy, using the mediastinoscope, produced good visualization of large areas of the parietal, visceral and diaphragmatic pleura in two patients and allowed adequate biopsy studies of the pleural nodules. At thoracotomy or thoracoscopy the pleura appears as a thickened, nodular rind, constricting and compressing the lung. A typical specimen removed by total pleurectomy is shown in Figure 3.

Results

Results of treatment of diffuse pleural mesothelioma are shown in Figure 4. The average length of survival after diagnosis was 15 months. One patient, who had been treated by total pleurectomy, survived for five years without evidence of recurrent tumor but subsequently died of a primary adenocarcinoma of the lung. Chemotherapy in 15 patients consisted of various combinations of doxorubicin, vincristine, cyclophosphamide, actinomycin-D, rubidazone and dacarbazine; however, these drugs did not appear to significantly alter the progression of the disease. Radiotherapy also appeared to be of little benefit in seven patients.

Discussion

The present series of patients bears out the strong relationship of pleural mesothelioma to asbestos exposure and probably reflects the substantial shipyard activity in the Puget Sound area. The long latency—32 years—between last known exposure and diagnosis is in agreement with other series and is of concern because significant exposure to abestos by certain occupational groups still continues.[7]

Since Wagner and co-workers first reported the relationship between asbestos exposure and mesothelioma in 1960, numerous reports have appeared describing the high incidence, not only of mesothelioma, but also of bronchogenic, oropharyngeal, laryngeal, gastrointestinal and renal tumors among those who have been exposed to asbestos.[1-5,9] Lung cancer death rates may be increased to 60 times those of controls by asbestos exposure and cigarette smoking.[9] Mesothelioma,

TABLE 2.—*Method of Diagnosis in 25 Patients With Diffuse Pleural Disease*

Method	*No. of Patients*
Thoractomy	19
Needle biopsy of pleura (5 attempted)	1
Cytology (11 attempted)	1
Thoracoscopy	2
Unknown	2

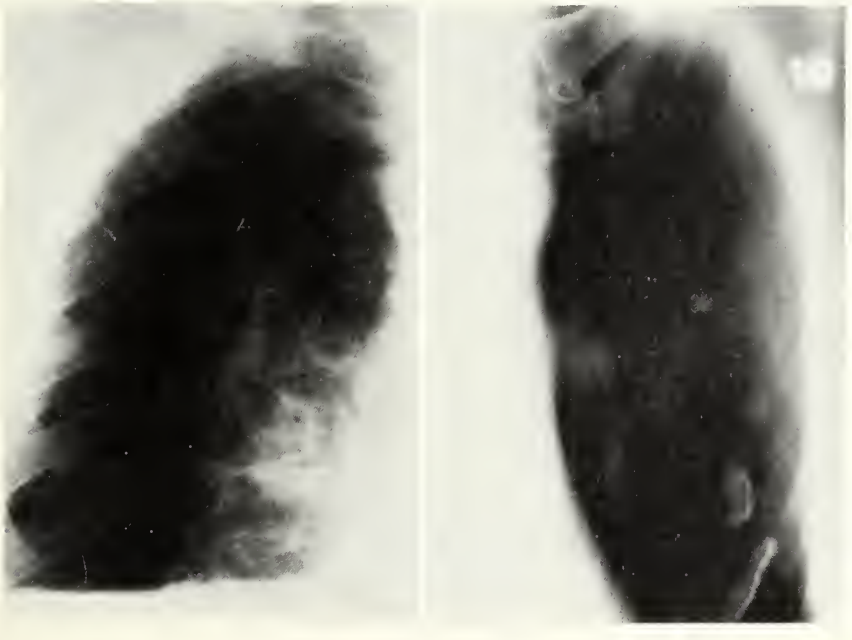


Figure 2.—X-ray studies of the chest showing typical findings in diffuse pleural mesothelioma: pleural effusion, pleural nodules and pleural plaques.

however, has no appearant relationship to cigarette smoking.[3]

Solitary benign tumors have not been shown to be related to asbestos exposure and are almost always cured by local resection.[10-12] Their major significance is in the occasional production of local symptoms and the difficulty of differentiating them from malignant lesions of the lung or mediastinum.

Peritoneal mesothelioma has a worse prognosis than diffuse pleural disease, with an average survival rate of three months to a year following diagnosis.[13,14] As occurred in this series, however, there may be an occasional patient with a predominant mass that resembles mesothelioma histologically, who may be cured by resection of the tumor combined with chemotherapy and radiation.

Although others have reported good results in diagnosing diffuse pleural disease by obtaining blind needle biopsies of the pleura or doing cytologic studies of pleural fluid,[6,15,16] these techniques were not productive in the present series. Thoracotomy was used to make the diagnosis in most patients in this group, although, recently, thoracoscopy was used successfully with minimal morbidity in two patients. The latter is certainly not a new procedure and has been reported previously in the diagnosis of mesothelioma; however, this is the first known report using a rigid mediastinoscope.[17]

Although the survival rate of the patients in our series is similar to that of others, these studies represent a somewhat heterogenous approach to therapy by a number of physicians.[6,15,16] Wanebo and colleagues,[18] using pleurectomy with or without radiation and chemotherapy, reported 5-year survival of 5 of 33 patients with diffuse pleural mesothelioma. DeLaria and co-workers[19] reported 11 patients having radical pleuropneumonectomy, with two surviving after two and four years, respectively. Schlienger and colleagues[20] reported a median survival of 13 months in patients treated with megavoltage radiotherapy to one hemithorax compared with 9.8 months survival in those receiving no radiation. Chemotherapy, using doxorubicin in combination with various other drugs, has been reported to induce a response rate of 20 percent to 40 percent in some patients.[21-23] Thus, there is evidence that all three modalities—surgical procedures, radiation and chemotherapy—

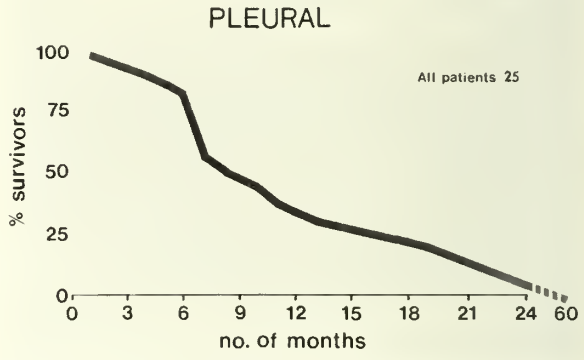


Figure 4.—Survival curve of all 25 patients with diffuse pleural mesothelioma, ranging from 2 to 60 months from time of diagnosis.

Figure 3.—Gross specimen of diffuse pleural mesothelioma, removed by total pleurectomy, showing irregular, fibronodular appearance of pleura.

may benefit patients with pleural mesothelioma. Intensive combined therapy using all three modalities is under way as an intercooperative group study, involving pleurectomy (recommended) and radiotherapy to 4,700 rads with or without doxorubicin therapy. (Written communication, June 1980; L. Wasser, L. Baker and M. Samson: Radiotherapy With and Without Chemotherapy for Malignant Pleural Mesothelioma Localized to One Hemithorax [Intergroup Mesothelioma Study] Eastern and Southwest Oncology Groups.) We recommend this protocol. Only with a prospective randomized clinical trial will the effects of the combined-modality treatment be measurable.

REFERENCES

1. McDonald JC, MacDonald AD: Epidemiology of mesothelioma from estimated incidence. Prevent Med 6:426-446, 1977

2. Wagner JC, Sleggs CA, Marchand P: Diffuse pleural mesothelioma and asbestos exposure in the Northwestern Cape Province. Br J Industr Med 17:260-270, 1960

3. Theriault GP, Grand-Bois L: Mesothelioma and asbestos in the Province of Quebec, 1969-1972. Arch Environ Health 33:15-19, Jan-Feb 1978

4. Newhouse ML, Berry G: Predictions of mortality from mesothelial tumors in asbestos factory workers. Br J Industr Med 33: 147-151, Aug 1976

5. Borrow M, Conston A, Livornese L, et al: Mesothelioma following exposure to asbestos: A review of 72 cases. Chest 64: 641-646, Nov 1973

6. Edge JR, Choudhury SL: Malignant mesothelioma of the pleura in Barrow-in-Furness. Thorax 33:26-30, Feb 1978

7. Chovil A, Stewart C: Latency period for mesothelioma. Lancet 2:853, Oct 20, 1979

8. Hinds MW: Mesothelioma in the United States—Incidence in the 1970s. J Occupat Med 20:469-471, Jul 1978

9. Selikoff IJ, Hammond EC: Asbestos and smoking (Editorial). JAMA 242:458, Aug 3, 1979

10. Scharifker D, Kaneko M: Localized fibrous "mesothelioma" of pleura (submesothelial fibroma)—A clinicopathologic study of 18 cases. Cancer 43:627-635, Feb 1979

11. Shabanah FH, Sayegh SF: Solitary (localized) pleural mesothelioma—Report of two cases and review of the literature. Chest 60:558-563, Dec 1971

12. Utley JR, Parker JC, Hahn RS, et al: Recurrent benign fibrous mesothelioma of the pleura. J Thorac Cardiovasc Surg 65:830-834, May 1973

13. Kannerstein M, Churg J: Peritoneal mesothelioma. Human Pathol 8:83-94, Jan 1977

14. Jones DEC, Silver D: Peritoneal mesothelioma. Surgery 86:556-560, Oct 1979

15. Ratzer ER, Pool JL, Melamed MR: Pleural mesotheliomas—Clinical experiences with thirty-seven patients. Am J Roentgenol 99:863-880, Apr 1967

16. Oels HC, Harrison EG, Carr DT, et al: Diffuse malignant mesothelioma of the pleura: A review of 37 cases. Chest 6:564-570, Dec 1971

17. Boushy SF, North LB, Helgason AA: Thoracoscopy: Technique and results in eighteen patients with pleural effusion. Chest 74:386-389, Oct 1978

18. Wanebo HJ, Martini N, Melamed MR, et al: Pleural mesothelioma. Cancer 38:2481-2488, Dec 1976

19. DeLaria GA, Jensik R, Faber LP, et al: Surgical management of malignant mesothelioma. Ann Thorac Surg 26:375-382, Oct 1978

20. Schlienger M, Eschwege F, Blache R, et al: Mesotheliomes pleuraux malins. Bull Cancer (Paris) 56:265-308, 1969

21. Spremulli E, Wampler G, Regelson W, et al: Chemotherapy of malignant mesothelioma. Cancer 40:2038-2045, Nov 1977

22. Yap B, Benjamin RS, Burgess MA, et al: The value of adriamycin in the treatment of diffuse malignant pleural mesothelioma. Cancer 42:1692-1696, Oct 1978

23. Chahinian AP, Suzuki Y, Mandel EM, et al: Diffuse pulmonary malignant mesothelioma—Response to doxorubicin and 5-azacytidine. Cancer 42:1687-1691, Oct 1978

Runners' Foot Problems

RUNNERS' FOOT PROBLEMS are interesting and come to our attention more frequently than ever before. . . . The orthotics developed by podiatrists, which orthopedists have come to accept, are effective treatment for many of the minor foot problems. They are firm metatarsal inserts that give a great deal of support and prevent the microcollapse that may occur in runners at the joints of the hindfoot and forefoot.

—ARNOLD T. BERMAN, MD, *Philadelphia*

Extracted from *Audio-Digest Internal Medicine,* Vol. 27, No. 13, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1577 East Chevy Chase Drive, Glendale, CA 91206.

Refer to: Donegan E, Deal MM, Melanephy MC, et al: Primary isolation of a new strain of the TATLOCK/Pittsburgh pneumonia agent (*Legionella micdadei*). West J Med 134:384-389, May 1981

Primary Isolation of a New Strain of the TATLOCK/Pittsburgh Pneumonia Agent *(Legionella micdadei)*

ELIZABETH A. DONEGAN, MD; MARLENE M. DEAL, PhD, *and* M. CLAIRE MELANEPHY, BS, *San Francisco*

LESTER G. CORDES III, MD, *and* C. WAYNE MOSS, PhD, *Atlanta*

VINCENT G. PONS, MD, *and* GEORGE F. BROOKS, MD, *San Francisco*

Pneumonia, empyema and lung abscesses developed in a patient following a neurosurgical procedure and associated short-term corticosteroid therapy. An organism identical to the TATLOCK/Pittsburgh pneumonia agent (Legionella micdadei) *was the only organism isolated from multiple specimens from lung aspirates and chest tube drainage. The organism was isolated directly on charcoal yeast extract (CYE) agar and classified as identical to the TATLOCK bacterium by direct immunofluorescent staining and by gas-liquid chromatography of cellular fatty acids. The patient's pulmonary infection improved during treatment with penicillin. Serum specimens obtained from the patient during convalescence showed an indirect fluorescent antibody reciprocal titer of 16,000 to his homologous antigen, but he also had titers that were potentially diagnostic against antigens of the six serogroups of* Legionella pneumophila *and three other* Legionella*-like organisms.* Legionella *can be isolated from clinical specimens by the routine use of CYE agar, which should be incorporated as the primary isolation medium for chest fluids and lung specimens. It appears that a large battery of antigens will be required for serological testing to diagnose infections caused by* L micadei, L pneumophila *and* Legionella*-like organisms.*

THE TATLOCK/PITTSBURGH PNEUMONIA AGENT is a Gram-negative bacillus phenotypically similar to *Legionella pneumophila*.[1] This organism is representative of a new species of *Legionella* for which the name *Legionella micdadei* sp nov has been proposed.[2] Another strain of *L micdadei*, the Pittsburgh pneumonia agent,[3] has been reported to be the etiologic agent in opportunistic pneumonias of immunosuppressed patients, particularly recipients of renal transplants.[4-6] The name *Legionella pittsburgensis* sp nov also has been proposed for this species.[7] In this report, we

From the Departments of Laboratory Medicine (Donegan, Deal, Melanephy and Brooks) and Medicine (Pons and Brooks), University of California, San Francisco; the Bureau of Epidemiology (Cordes) and the Bureau of Laboratories (Moss), US Public Health Service, Center for Disease Control, Atlanta.

Submitted June 23, 1980.

Reprint requests to: George F. Brooks, MD, Department of Laboratory Medicine, U-230 (M-506), University of California San Francisco, San Francisco, CA 94143.

ABBREVIATIONS USED IN TEXT

CYE=charcoal yeast extract (agar)
DFA=direct fluorescent antibody
GLC=gas-liquid chromatography
IFA=indirect fluorescent antibody
LLO=*Legionella*-like organisms
Pi-1=Pittsburgh 1 (strain)
SF-1=San Francisco 1 (strain)
SBA=sheep blood agar

describe a case of pneumonia, the direct isolation of a new strain of *L micdadei* on solid media, and the patient's serological responses to *L micdadei, L pneumophila* and some *Legionella*-like organisms (LLO).

Report of a Case

A 60-year-old man was admitted to hospital for an elective surgical procedure to relieve a right hemifacial spasm that had developed six years earlier. On the third day in hospital, a suboccipital craniectomy of the right side and microvascular decompression of the right facial nerve were carried out. Following the operation, the patient was noted to have paresis of the cranial nerves VII, IX and X of the right side. Dysphagia and regurgitation occurred; however, the patient stated that he had not aspirated the oral secretions.

On hospital day 2 he had received a total dose of 20 mg of dexamethasone (Decadron) followed by 16 mg of the drug on days 3 through 8, with tapering to 8 mg on days 9 and 10 and 1 mg on day 11 when he was discharged.

On day 14 he was readmitted to hospital because of cough and fever. His blood pressure was 130/70 mm of mercury, pulse 100 per minute and temperature 39°C (102.2°F) (see Figure 1). Rales were heard over both lung bases. Paresis of the VII, IX and X cranial nerves of the right side persisted. A roentgenogram of the chest showed hazy densities in the basilar segments of the left lower lobe and superior segment of the right lower lobe, with elevation of the left diaphragm. The leukocyte count was 13,200 per cu mm, with 94 percent polymorphonuclear leukocytes. An expectorated sputum specimen showed numerous polymorphonuclear leukocytes on Gram stain. The patient was thought to have pneumonia resulting from aspiration of oral secretions, and 2,000,000 units of penicillin G were administered intravenously every four hours. Intravenous hydration, chest physiotherapy and nasal oxygen were administered as well. He remained febrile with daily elevations of temperature to 39.5°C (103.1°F).

On day 17, clindamycin, 600 mg given intravenously every six hours, was added to the patient's regimen. On day 20, a roentgenogram of the chest showed more infiltrates in both the right and left lower lobes. An air-fluid level thought to represent an empyema or abscess was also noted in the right lower lung field, and a left pleural effusion was present. On day 21, a chest tube inserted in the left posterior lobe yielded 250 ml of purulent material. By day 30, the right lower lobe mass had increased in size and cavitation was evident (Figure 2). On day 32, two chest tubes were placed in the right side of the chest and

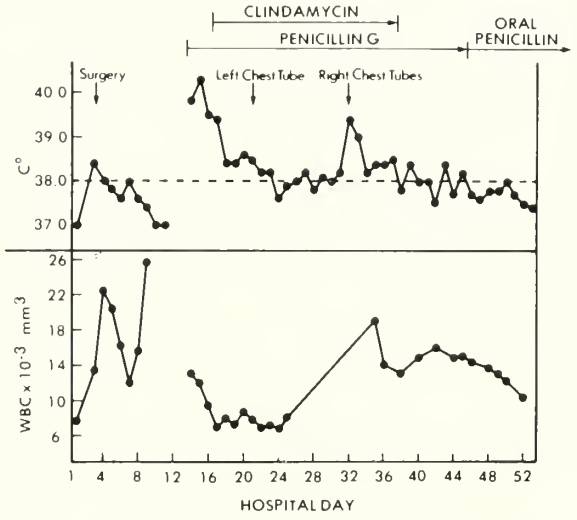


Figure 1.—Summary of hospital course. Daily maximum temperatures, leukocyte counts, antimicrobic therapy and significant procedures are noted.

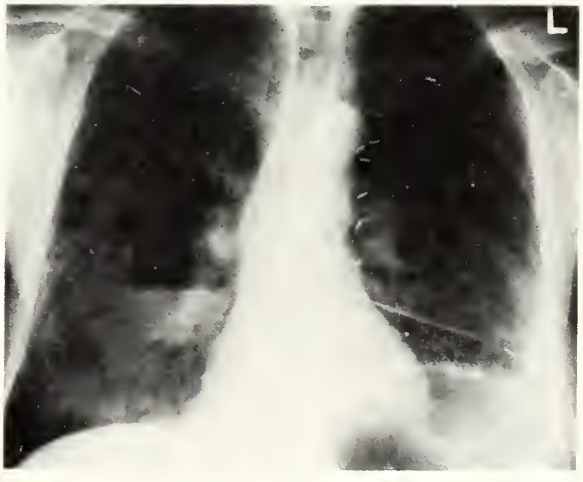


Figure 2.—A roentgenogram of the chest taken on the 30th hospital day.

yielded 100 ml of purulent material. The patient's leukocyte count had risen, but his peak daily temperature began to decrease (Figure 1). His condition appeared clinically improved and on day 37 clindamycin therapy was discontinued. By day 42, a roentgenogram of the chest showed improvement of the lung lesions. There was substantial clinical improvement and the chest tubes were advanced and removed. Intravenous penicillin therapy was stopped on day 48 and oral administration of phenoxymethyl penicillin, 1 gram every six hours, was begun. The patient was discharged from the hospital on day 54 and oral penicillin therapy was continued until day 65. In all, he had received penicillin for 50 days. On day 79, a follow-up examination indicated that the patient's pulmonary infection was much improved, and a roentgenogram of the chest showed resolution of his parenchymal disease and empyema.

Methods

Material recovered from aspiration of the right lung, bilateral chest tube drainage and bilateral thoracentesis was inoculated onto standard bacteriological media for the isolation of aerobic and anaerobic bacteria, mycobacteria and fungi. A charcoal yeast extract (CYE) agar plate was included for isolation of *L pneumophila*.[8] All routine aerobic media were incubated in 3 percent to 5 percent carbon dioxide at 35°C and were examined for growth at 24 and 48 hours after inoculation. All routine media were discarded after 48 hours if no growth had been observed. Anaerobic media were incubated in anaerobe jars that were flushed with gas two times and then filled with a gas mixture containing 85 percent nitrogen, 10 percent hydrogen and 5 percent carbon dioxide and incubated at 35°C for two days before examination. Plates showing no growth were discarded at this time. Test cultures for fungi were incubated at 35°C in 5 percent to 7 percent carbon dioxide for two days; the plates were examined daily for growth for a week and then weekly for a month. Test cultures for mycobacteria were incubated in 5 percent carbon dioxide at 35°C for eight weeks and examined weekly for growth. Smears of each clinical specimen were stained using Gram, auramine 0 and Ziehl-Neelsen techniques.

The CYE agar plates were incubated in a moist atmosphere in 5 percent to 7 percent carbon dioxide at 35°C for 14 days and were examined daily for growth. At the end of incubation, plates with no growth were discarded. Any colonies that had developed on the CYE agar were also tested for growth on sheep blood agar (SBA) plates. Those colonies that grew on CYE agar but not on SBA were subsequently tested for catalase and oxidase production, gelatin liquefaction, starch hydrolysis and β-lactamase production.

Organisms which grew only on CYE agar were tested using the direct fluorescent antibody (DFA) technique, with conjugates prepared against the six serogroups of *L pneumophila*,[9-11] as well as WIGA,[12] TATLOCK[1] and LLO.[13,14] Indirect fluorescent antibody (IFA) testing was used to obtain titers of three serum specimens drawn from the patient on days 50, 81 and 88.[15] Antigens used included the patient's isolate, *L micdadei* (strain Pi-1), six strains of *L pneumophila* (representing the six serogroups) and three LLO isolates.[12,14] All three serum specimens were run simultaneously against the 11 antigens; serological results were confirmed by a second set of tests done on a separate day.

The cells used for fatty acid analysis were grown for 24 to 48 hours on CYE agar and processed for cellular fatty acids as previously described.[16] The resulting fatty acid methyl esters were analyzed with gas-liquid chromatography (GLC) on a 3 percent OV-1 column (Applied Science Laboratory, State College, Pennsylvania), using a flame ionization detector. The conditions of GLC and mass spectrometry and the quantitation of methyl esters were done as described in earlier reports.[16-19]

Results

Multiple sputum specimens were cultured for bacteria, mycobacteria and fungi. Mixtures of normal oronasal flora were grown with an occasional specimen containing predominantly Gram-negative rods (*Klebsiella pneumoniae, Enterobacter cloacae, Citrobacter freundii*) or *Candida tropicalis*, or both. Specimens of chest tube drainages, empyema of the left and right sides, aspirates from the right side of the chest and pleural fluid from the left lung were all negative when cultured for mycobacteria and fungi.

All specimens except the purulent material from the tube in the right posterior side of the chest (obtained during insertion on day 32) were negative when cultured for aerobic and anaerobic bacteria. After ten days of incubation the culture of the chest tube drainage specimen showed a few colonies growing only on the CYE agar plate. These organisms were long, slender, Gram-negative rods

TABLE 1.—*Reciprocal Indirect Immunofluorescent Antibody Titers of the Patient's Sera Tested Against* Legionella micdadei, L pneumophila *and* Legionella-*like Organisms*

Antigen	*Reciprocal Serum Titers on Days* 50	81	88
*Legionella micdadei**			
SF-1	8,000	16,000	16,000
Pi-1	16,000	16,000	16,000
Legionella pneumophila†			
Philadelphia 1 (1)	256	256	256
Togus 1 (2)	256	256	256
Bloomington 2 (3)	1,024	512	512
Los Angeles 1 (4)	512	512	512
Dallas 2E (5)	512	512	512
Chicago 2 (6)	512	256	512
Legionella-like organisms‡			
WIGA	256	256	128
LS-13	256	256	256
NY-23	512	256	256

*SF-1 = San Francisco 1; Pi-1 = Pittsburgh 1
†Number in parentheses = serogroup of *L pneumophila*
‡WIGA, LS-13, NY-23 (see references 12 and 14)

that were positive for catalase production, oxidase production and gelatin liquefaction, negative for starch hydrolysis and positive for acid-fast staining using the modified Ziehl-Neelsen method. The Ziehl-Neelsen and auramine 0 stains for mycobacteria were negative. The cultured organism was later identified by the Center for Disease Control (CDC) as a β-lactamase-negative bacterium identical to the TATLOCK bacterium. When this organism was tested by the DFA method with conjugates for *L pneumophila* (six serogroups), WIGA and some *Legionella*-like organisms, no fluorescence was observed. When the culture was tested by the DFA method with the TATLOCK conjugate,[1] many fluorescent bacteria were observed. This isolate was designated *Legionella micdadei,* San Francisco 1 (SF-1).

The results of indirect immunofluorescent tests of the patient's serum specimens obtained on days 50, 81 and 88 are presented in Table 1. Our patient's specimens showed reciprocal titers of at least 256 on day 50 to all of the *Legionella pneumophila* reference strains and to reference *Legionella*-like organisms. There was a titer of 1,056 to one of the *Legionella pneumophila* strains from serum drawn on day 50. However, the patient's titers to *L micdadei,* including the San Francisco isolate (SF-1) and the reference CDC isolate from Pittsburgh (Pi-1), were much higher (8,000 to 16,000). No significant fall in titer was noted between day 50 and day 88.

The GLC cellular fatty acid profile of the SF-1 isolate is shown in Figure 3. The single most abundant acid was a saturated branched-chain 15-carbon acid (a-15:0) and the second most abundant acid was a saturated branched-chain 17-carbon acid (a-17:0). The point-of-branching of the methyl group of each of these acids was established by mass spectrometry to be at the anteiso (antepenultimate) carbon atom. A small amount (approximately 4 percent) of a monounsaturated branched-chain 17-carbon acid (a-17:1) also was present. The a-17:1 acid has been observed in the TATLOCK, HEBA[1] and Pi-1 bacteria[3] but has not been detected in the *L pneumophila*[18] or the WIGA bacterium.[19] Thus, TATLOCK, HEBA, Pi-1 and SF-1 were identical by cellular fatty acid composition; however, each was distinguished from *L pneumophila* and other *Legionella*-like organisms by the presence of small amounts of the a-17:1 acid.

Discussion

Clinically, this patient's pulmonary disease appeared to be secondary to aspiration of oral-pharyngeal contents, with the development of progressive pneumonia and lung abscesses. Al-

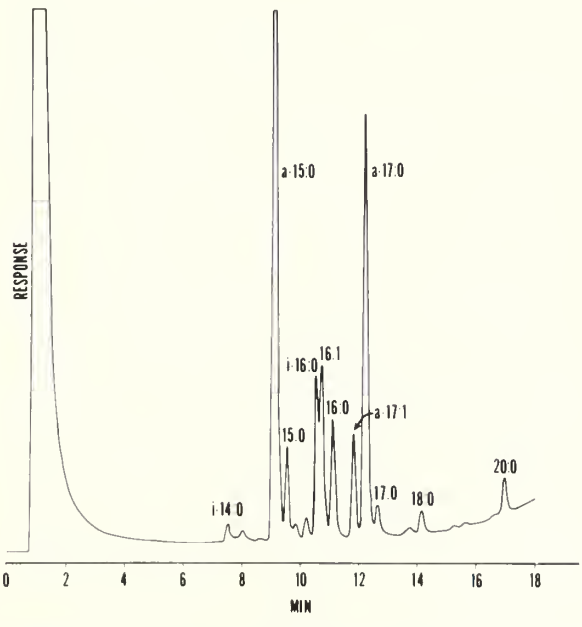


Figure 3.—Gas-liquid chromatogram of esterfied fatty acids (as methyl ester) from saponified whole cells of the SF-1 isolate. Analysis was made on a 3 percent OV-1 column. Peak designations: the number before the colon refers to the number of carbon atoms; the number to the right refers to the number of double bonds, and "i" indicates a branched-chain acid with the methyl group at the antepenultimate carbon.

though there were no clinical or roentgenographic findings indicating an unusual cause for his disease, multiple cultures of empyema and lung abscess specimens yielded only the SF-1 isolate of *L micdadei*. Intervening antimicrobial therapy could have modified the culture results, but the isolation of the SF-1 bacterium, coupled with very high indirect immunofluorescent antibody titers in convalescent-phase serum specimens, is highly suggestive that this organism was a contributing cause of the patient's infection.

The roentgenographic findings of patients with *L micdadei* pneumonia have been variable.[5] Alveolar and nodular infiltrates and pleural effusions have been noted. Although cavitation was not recognized roentgenographically, abscesses were noted at postmortem examinations. Our patient had pulmonary infiltrates, pleural effusions and cavitation with air fluid levels, indicating that *L micdadei* may well be associated with the complete spectrum of pleural-pulmonary infections.

The cases described by Myerowitz and colleagues[5] involved immunosuppressed patients who had had renal transplants. Each had also had recent institution of daily high-dose corticosteroid therapy. Although our patient had corticosteroid therapy in association with his neurosurgical procedure, the duration of this therapy was probably not sufficient to provide a major immunosuppressive effect comparable with that of renal transplant patients. Our patient's corticosteroid therapy may have contributed to the development of pneumonia, while withdrawal of the corticosteroid on day 11 may have enhanced his ability to survive the infection.

The clinical spectrum of infection by *L micdadei* has not been defined. The isolates from a soldier at Fort Bragg[20,21] and from the case described by Bozeman and colleagues[22] were found in patients with varying clinical diseases. There is some evidence that "Fort Bragg fever" was in fact caused by *Leptospira*.[23] Recent cases have involved immunosuppressed patients in whom nosocomial infections developed.[4-6,24] In the hospital setting, it is unknown whether the organism is part of a patient's normal flora or acquired from the environment.

The geographical distribution of *L micdadei* may be very wide. The organism has been found in the southeastern, the northeastern and, now, the western portion of the United States. Whether or not it occurs in other parts of the world is not known.

Initially, it was thought that TATLOCK and the Pittsburgh pneumonia agent could be cultivated only in animals and in embryonated eggs. Recently, isolates in embryonated eggs derived from blood specimens of a Fort Bragg soldier and from lung tissue of a patient infected with the Pittsburgh pneumonia agent were grown on artificial media, indicating that the species can be isolated on solid media.[1,3] This finding has been confirmed by subsequent reisolation of the Pittsburgh bacteria from frozen lung tissue following a direct isolation from embryonated eggs.[7] The direct isolation of the SF-1 isolate on CYE agar media in our case indicates the potential value of routine inclusion of CYE agar in culture systems for pleural fluid and lung biopsy specimens. The clinical response in association with penicillin therapy, coupled with failure to show β-lactamase production in vitro, indicates that testing for β-lactamase also should be done. Direct fluorescent-antibody studies on the organism were useful in ruling out *Legionella pneumophila* and in identifying the organism as *L micdadei*.

Gas-liquid chromatographic analysis of cellular fatty acids has proved to be useful in distinguishing *L micdadei* from *L pneumophila* and other LLO.[2,16-19] In this case, the fatty acid composition of SF-1 was characteristic of *L micdadei*, including the small amount (4 percent) of a-17:1 which is apparently characteristic of this species (Figure 3). As has been emphasized in the past, fatty acid composition of bacteria can be influenced by a variety of growth conditions (such as media, temperature and age) that must be evaluated before interpretation.

Conclusion

The serological findings in our patient were striking and may have broad implications. The indirect immunofluorescent titer was approximately eight times higher than for any previously reported case of legionellosis. In association with the high titer to *L micdadei*, potentially diagnostic titers were seen for *L pneumophila* and other LLO. A fourfold or greater increase in reciprocal titer to 128 in acute and convalescent serum specimens or a single or standing reciprocal titer of 256 is considered presumptive evidence of *L pneumophila* infection[15] and could be considered presumptive evidence for LLO infections as well. Our patient's serum specimens had high standing titers for *L pneumophila* and LLO. His disease could have been thought to be caused by one or

all of these organisms had not further investigation yielded the SF-1 isolate and the high titer against *L micdadei.*

It appears that serological tests to diagnose infections caused by these organisms will require a large battery of antigens. It may be important for ten or more antigens to be used to accurately assess the cause of pneumonia. The 11 antigens used for our patient (six *L pneumophila,* three LLO and two *L micdadei*) may be the minimum number required. Careful consideration of serological cross-reactivity will also be important in understanding the roles of these agents as causes of disease.

REFERENCES

1. Hébert GA, Moss CW, McDougal LK, et al: The rickettsia-like organisms TATLOCK (1943) and HEBA (1959): Bacteria phenotypically similar to but genetically distinct from *Legionella pneumophila* and the WIGA bacterium. Ann Intern Med 92:45-52, 1980

2. Hébert GA, Steigerwalt AG, Brenner DJ: *Legionella micdadei* species nova: Classification of a third species of *Legionella* associated with human pneumonia. Curr Microbiol 3:255-258, 1980

3. Hébert GA, Thomason BM, Harris PP, et al: "Pittsburgh pneumonia agent": A bacterium phenotypically similar to *Legionella pneumophila* and identical to the TATLOCK bacterium. Ann Intern Med 92:53-54, 1980

4. Pasculle AW, Myerowitz RL, Rinaldo CR: New bacterial agent of pneumonia isolated from renal-transplant recipients. Lancet 2:58-61, 1979

5. Myerowitz RL, Pasculle AW, Dowling JN, et al: Opportunistic lung infection due to "Pittsburgh pneumonia agent." N Engl J Med 301:953-958, 1979

6. Rogers BH, Donowitz GR, Walter GK, et al: Opportunistic pneumonia: A clinicopathological study of five cases caused by an unidentified acid-fast bacterium. N Engl J Med 301:959-961, 1979

7. Pasculle AW, Feeley JC, Gibson LG, et al: Pittsburgh pneumonia agent: Direct isolation from human lung tissue. J Infect Dis 141:727-732, 1980

8. Gibson RJ, Gorman GW, Langford NC, et al: Charcoal-yeast extract agar: Primary isolation medium for *Legionella pneumophila.* J Clin Microbiol 10:437-441, 1979

9. McKinney RM, Thacker L, Harris PP, et al: Four serogroups of Legionnaires disease bacteria defined by direct immunofluorescence. Ann Intern Med 90:621-624, 1978

10. McKinny RM, Wilkinson HW, Sommers HM, et al: *Legionella pneumophila* serogroup six—Isolation from cases of legionellosis, identification by immunofluorescence staining, and immunologic response to infection. J Clin Micro 12:395-401, 1980

11. England AC, McKinney RM, Skaliy P, et al: A fifth serogroup of *Legionella pneumophila.* Ann Intern Med 93:58-59, 1980

12. Thomason BM, Harris PP, Hicklin MD, et al: A *Legionella*-like bacterium related to WIGA in a fatal case of pneumonia. Ann Intern Med 91:673-676, 1979

13. Lewallen KR, McKinney RM, Brenner DJ, et al: A newly identified bacterium phenotypically resembling, but genetically distinct from, *Legionella pneumophila:* An isolate in a case of pneumonia. Ann Intern Med 91:831-834, 1979

14. Cordes LG, Wilkinson HW, Gorman GW, et al: Atypical *Legionella*-like organisms: Fastidious water-associated bacteria pathogenic for man. Lancet 2:927-930, 1979

15. Wilkinson HW, Fikes BJ, Cruce DD: Indirect immunofluorescence test for serodiagnosis of Legionnaires' disease: Evidence for serogroup diversity of Legionnaires' disease bacterial antigens and for multiple specificity of human antibodies. J Clin Microbiol 9:379-383, 1979

16. Moss CW, Weaver RE, Dees SB, et al: Cellular fatty acid composition of isolates from Legionnaires' disease. J Clin Microbiol 6:140-143, 1977

17. Moss CW, Dees SB: Identification of microorganisms by gas chromatographic-mass spectrometric analysis of cellular fatty acids. J Chromatogr 112:595-604, 1975

18. Moss CW, Dees SB: Further studies of the cellular fatty acid composition of Legionnaires' disease bacteria. J Clin Microbiol 10:437-441, 1979

19. Moss CW, Dees SB: Cellular fatty acid composition of WIGA, a rickettsia-like agent similar to Legionnaires' disease bacterium. J Clin Microbol 10:390-391, 1979

20. Daniels WB, Grennan HA: Pretibial fever—An obscure disease. JAMA 122:361-365, 1943

21. Tatlock H: A rickettsia-like organism recovered from guinea pigs. Proc Soc Exp Biol Med 57:95-99, 1944

22. Bozeman FM, Humphries JW, Campbell JM: A new group of rickettsia-like agents recovered from guinea pigs. Acta Virol (Praha) 12:87-93, 1968

23. Gochenour WS Jr, Smadel JE, Jackson EB, et al: Leptospiral etiology of Fort Bragg fever. Pub Health Rep 67:811-813, 1952

24. Thomason BM, Ewing EP, Hicklin MD, et al: TATLOCK bacterium (Pittsburgh pneumonia agent) presumptively identified in five cases of pneumonia. Ann Intern Med 92:510, 1980

Refer to: Hepner GW, Piken E, Lechago J: Abnormal aminopyrine metabolism in patients with chronic hepatitis. West J Med 134:390-393, May 1981

Abnormal Aminopyrine Metabolism in Patients With Chronic Hepatitis

GERSHON W. HEPNER, MD; EDWARD PIKEN, MD, *and*
JUAN LECHAGO, MD, PhD, *Torrance, California*

Aminopyrine metabolism was studied by the aminopyrine breath test in 21 control subjects, 24 patients with untreated chronic active hepatitis (CAH), 4 patients with treated CAH and 17 patients with chronic persistent hepatitis (CPH). Aminopyrine breath tests gave abnormal results in 20 of 24 patients with untreated CAH. Findings were normal in all patients with treated CAH or with CPH. This test may be helpful in discriminating between CAH and other forms of chronic hepatitis.

CHRONIC ACTIVE HEPATITIS has a wide spectrum of clinical and histological severity.[1] In many patients, the course is progressive but may be affected by drugs such as prednisone or azathioprine.[2-5] In others, the disease may progress slowly, if at all. In contrast, persistent hepatitis nearly always has a benign prognosis and requires no therapy.[6] We have previously reported that hepatic N-demethylation of aminopyrine labeled with carbon 14, determined by the aminopyrine breath test (ABT), is impaired in most patients with cirrhosis[7,8] or hepatic neoplasm,[8,9] and this has been confirmed by other investigators.[10-12] We therefore carried out a study to determine whether it could be of any assistance in discriminating between patients with different forms of chronic hepatitis. Our data suggest that results of an ABT are always normal in patients with chronic persistent hepatitis (CPH) and nearly always abnormal in patients with untreated chronic active hepatitis (CAH).

From the Division of Gastroenterology and the Department of Pathology, Harbor-UCLA Medical Center, Torrance, California.

Submitted, revised, November 24, 1980.

Reprint requests to: Gershon W. Hepner, MD, 2080 Century Park East, Suite 903, Los Angeles CA 90067.

Patients and Methods

Patients

The patients in the study included 21 control subjects without liver disease, 24 patients with chronic active hepatitis and 17 patients with chronic persistent hepatitis. In all patients in the last two groups the diagnoses were made by liver biopsy carried out within two weeks of the aminopyrine breath test. The control subjects included 11 men and 10 women, median age 44, and none of them had any history of liver disease or had taken any drugs, including alcohol, for at least two weeks before the study. Of the controls, six had rheumatoid arthritis, eight had peptic ulcer disease, four had hypertension and three had reflux esophagitis. The patients with CAH included 14 who were positive for hepatitis B surface antigen (HBsAg), all with a previous history of

ABBREVIATIONS USED IN TEXT

ABT = aminopyrine breath test
CAH = chronic active hepatitis
CPH = chronic persistent hepatitis
HBsAg = hepatitis B surface antigen

intravenous drug abuse, plus two other HBsAg-negative subjects who had also had a previous history of drug abuse. The patients with CPH included eight who were HBsAg-positive, all of whom had a history of intravenous drug abuse. As far as could be determined, none of the patients with liver disease had taken any drugs, including alcohol, methadone or barbiturates, for at least two weeks before the aminopyrine breath test.

Second aminopyrine breath tests were done on a number of subjects. In four control subjects with rheumatoid arthritis studies were done twice, once before starting therapy with prednisone, 20 mg per day, and again after one month of this therapy. Studies were done twice in four patients with CAH, once before starting prednisone therapy and again, 6 to 12 months later, while they were taking prednisone but were in apparent remission from their CAH. These four patients all were found to have cirrhosis in pretreatment liver biopsy studies; posttreatment liver biopsy studies showed remission of the disease. To assess the reproducibility of the ABT, tests were done twice in six patients with untreated CAH at intervals of one week.

The clinical and biochemical features of the patients with CAH and CPH at the time of the study are illustrated in Table 1. The two groups differed significantly in only two features, serum bilirubin and gamma globulin values, both of which were higher in the patients with CAH than in those with CPH. Of 21 patients with CAH, 9 had serum bilirubin values greater than 2.0 mg per dl in contrast to only 3 of 17 patients with CPH. Gamma globulin values were greater than 1.5 grams per dl in 6 of 10 patients with CAH and in none of the 11 patients with CPH in whom this was determined. We excluded from the studies patients with ascites or encephalopathy because we felt that in such patients no special studies such as an aminopyrine breath test are necessary to determine whether or not the patient has chronic active liver disease.

TABLE 1.—*Initial Features in Chronic Active Liver Disease*

	CAH	CPH
Clinical features		
Sex, male	15	12
Age, year (median)	40	36
Time since diagnosis, months (median)	16	13
Biochemical features		
Albumin, grams/dl (median)	3.4	3.8
Bilirubin, mg/dl (median)	2.3	0.9*
Serum aspartate aminotransferase (SGOT), IU/liter (median)	164.0	178.0
Prothrombin time, percent normal (median)	92.0	100.0
Gamma globulin, grams/dl (median†)	2.2	1.4*

CAH = chronic active hepatitis
CPH = chronic persistent hepatitis

*$P < 0.01$.
†Determined in 10 patients with CAH and in 11 patients with CPH.

Histological Studies

Liver biopsy specimens were stained by conventional techniques and examined by one of us (J.L.) without reference to the clinical or biochemical status of the patient or the aminopyrine breath test. The criteria for diagnosing CAH included chronic inflammation in portal areas, significant piecemeal necrosis, regeneration of hepatocytes and, occasionally, bridging necrosis. In addition, 10 of 24 patients with CAH had extensive nodular regeneration and fibrosis, such that cirrhosis was the dominating feature. CPH, on the other hand, was characterized by absence of parenchymatous damage and presence of moderate portal inflammation without piecemeal necrosis.

Aminopyrine Breath Test

Aminopyrine breath tests were carried out as previously described.[7] Briefly, this test involves oral administration of a trace dose (1 to 2 μCi) of aminopyrine labeled with carbon 14 (Amersham, Chicago, Illinois), followed after two hours by collection of a single sample of breath, 2 mmole of carbon dioxide, in duplicate vials containing 2 mmole ethanolic hyamine with thymolphthalein as indicator. The specific activity of breath carbon dioxide tagged with carbon 14 ($^{14}CO_2$) is determined by counting the ethanolic hyamine in a liquid scintillation counter after addition of a liquid scintillation cocktail. Output of breath $^{14}CO_2$ in two hours is determined by multiplying mean $^{14}CO_2$ specific activity by the endogenous output of carbon dioxide (mmoles per kg of body weight per hour).[14] The data are

then expressed as the percentage of administered carbon 14 excreted in breath $^{14}CO_2$ in two hours (ABT). In previous studies, we have shown that the ABT correlates with the metabolic clearance rate of aminopyrine in control subjects[7,15] and in patients with hepatocellular disease,[7,14] hepatic neoplasm,[8,9] cholestasis[16] or congestive cardiac failure.[17] To minimize variability of data due to variability of endogenous carbon dioxide output,[18,19] all subjects were studied while nonambulant and fasting.

Serum Biochemistry

Determinations of serum albumin, bilirubin, aspartate aminotransferase (SGOT) and alanine aminotransferase (SGPT) were carried out by an automated method using the Vickers M-300. Gamma globulin values were found by cellulose acetate electrophoresis. Prothrombin time was determined using an automatic method using the Electra 600.

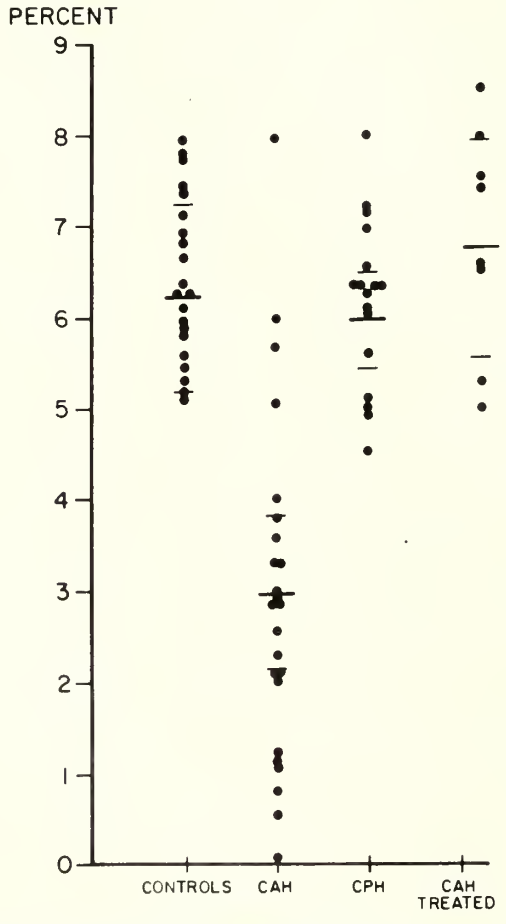


Figure 1.—Results of aminopyrine breath tests in the patients studied.

Statistics

Comparisons between controls and patients with liver disease were made by analysis of variance. Comparisons between patient groups were made using Student's *t* test. Where appropriate, a paired *t* test was done.

Results

The ABT in the patients studied is shown in Figure 1. It was 6.3 ± 1.09 percent (mean $\pm$ SD) in the control subjects, similar to values in control subjects obtained in our previous studies.[6-8,10-12] In the patients with CAH, the ABT was 3.0 ± 1.8 percent, significantly lower than in the control subjects ($P < 0.001$). In the patients with CPH the ABT was 6.0 ± 1.5 percent, similar to that in the controls ($P > 0.1$). The ABT in the patients with CAH was not significantly different in patients with CAH having cirrhosis (2.6 ± 1.6 percent) and those without cirrhosis (3.1 ± 2.0 percent) ($P > 0.1$) and not significantly different in the HBsAg-positive patients (3.3 ± 2.4 percent) and

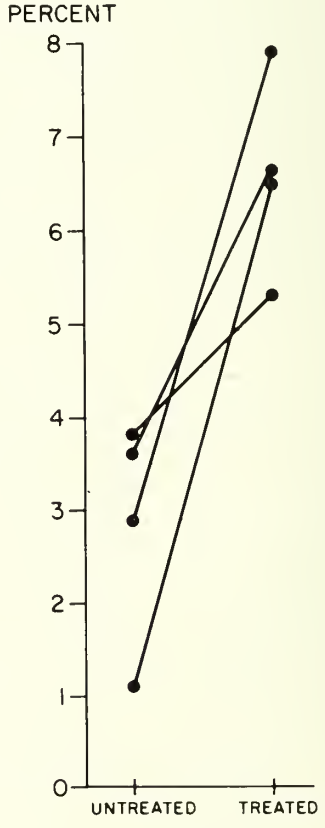


Figure 2.—Results of aminopyrine breath tests in patients with chronic liver disease before and after treatment with prednisone.

the HBsAg-negative patients (3.4±2.1 percent) ($P>0.1$).

In all four patients with CAH studied twice, before and after prednisone therapy, the ABT results returned to normal after therapy (Figure 2). In the six patients with untreated CAH studied twice, at intervals of three to seven days, the ABT results did not change significantly (first ABT 3.5±2.0 percent; second ABT 3.7±2.1 percent, $P>0.1$). The ABT did not change significantly in the four patients with rheumatoid arthritis studied before therapy with prednisone (6.2±1.3 percent) and one month after starting therapy (6.5±1.6 percent) ($P>0.1$).

Discussion

The ABT findings were normal in our study in all patients with CPH. In contrast, they were abnormal in 20 of 24 patients with CAH. Thus, the data suggest that the ABT may be helpful in evaluating patients with chronic hepatitis. An abnormal ABT result was never found in cases of CPH, and hence in patients with chronic hepatitis it would strongly suggest CAH.

The reason for the abnormal ABT finding in patients with CAH in contrast to that in patients with CPH is unclear. It may have been related to cirrhosis, which is often undetected by needle biopsy in these patients even when it is, in fact, present. It is also possible that there is more hepatic microsomal damage in CAH patients, even without cirrhosis, than in patients with CPH, but such differences have not been observed morphologically. Another possibility is that there is decreased hepatic aminopyrine uptake in these patients, possibly related to portal-systemic shunting.

The improvement of the ABT results in patients with CAH treated with prednisone supports the data from other studies that corticosteroids may be useful in treating this condition. The ultimate verification of this hypothesis will depend on long-term follow-up studies.

In conclusion, the study indicates that in patients with chronic hepatitis and an abnormal ABT finding the diagnosis is extremely likely to be CAH. The potential usefulness of this observation in the workup of patients with chronic hepatitis needs to be evaluated in a prospective study.

REFERENCES

1. Berk PD, Jones EA, Plotz PH, et al: Corticosteroid therapy for chronic active hepatitis. Ann Intern Med 85:523-525, 1976

2. Cook GC, Mullingan R, Sherlock S: Controlled prospective trial of corticosteroid therapy in active chronic hepatitis. Q J Med 40:159-185, 1971

3. Soloway RD, Summerskill WHH, Baggenstoss AH, et al: Clinical, biochemical and histological remission of severe, chronic active liver disease: A controlled study of treatment and early prognosis. Gastroenterology 63:820-833, 1972

4. Murrary-Lyon IM, Stern RB, Williams R: Controlled trial of prednisone and azathioprine in active chronic hepatitis. Lancet 1:735-737, 1973

5. Wright EC, Seeff LB, Berk PD, et al: Treatment of chronic active hepatitis—An analysis of three controlled trials. Gastroenterology 73:1422-1430, 1977

6. Chadwick RG, Galizzi J, Heathcote EJ, et al: Natural history of chronic persistent hepatitis. Gut 18:951, 1977

7. Hepner GW, Vesell ES: Quantitative assessment of hepatic function by breath analysis after oral administration of [^{14}C] aminopyrine. Ann Intern Med 83:632-639, 1975

8. Hepner GW, Vesell ES, Lipton A, et al: Disposition of aminopyrine, antipyrine, diazepam and indocyanine green in patients with liver disease or on anticonvulsant therapy: Diazepam breath test and correlation in drug elimination. J Lab Clin Med 90:440-456, 1977

9. Hepner GW, Uhlin SR, Harvey HA, et al: Abnormal aminopyrine metabolism in patients with hepatic neoplasm—Detection by breath test. JAMA 236:1587, 1976

10. Bircher J, Kupfer A, Gikalov I, et al: Aminopyrine demethylation measured by breath analysis in cirrhosis. Clin Pharmacol Ther 20:484-492, 1976

11. Galizzi J, Long JG, Billing BH, et al: Assessment of the (^{13}C) aminopyrine breath test in liver disease. Gut 19:40-45, 1978

12. Carlisle R, Galambos JT, Warren WD: The relationship between conventional liver tests, quantitative function tests and histopathology in cirrhosis. Dig Dis Sci 24:358-362, 1979

13. Koretz RL, Lewin KJ, Rebhun DJ, et al: Hepatitis B surface antigen carriers—To biopsy or not to biopsy. Gastroenterology 75:860-863, 1978

14. Winchell HS, Stahelin H, Kusubov N, et al: Kinetics of CO_2-HCO_3 in normal adult males. J Nucl Med 11:711-715, 1970

15. Hepner GW, Vesell ES: Aminopyrine disposition: Studies on breath, saliva and urine of subjects and patients with liver disease. Clin Pharmacol Ther 20:654-660, 1976

16. Hepner GW, Vesell ES: Aminopyrine metabolism in the presence of hyperbilirubinemia due to cholestasis or hepatocellular disease: Combined use of laboratory tests to study disease-induced alterations in drug disposition. Clin Pharmacol Ther 21:213-216, 1977

17. Hepner GW, Vesell ES, Tantum KR: Reduced drug elimination in congestive heart failure: Studies using aminopyrine as a model drug. Am J Med 65:271-276, 1978

18. Hepner GW, Vesell ES: Assessment of aminopyrine metabolism in man after oral administration of ^{14}C-aminopyrine: Effects of phenobarbital, disulfiram and portal cirrhosis. N Engl J Med 291:1384-1388, 1974

19. King C, Toskes P: A caveat: Endogenous CO_2 production increases during non-fasting carbon isotope breath tests. Gastroenterology 74:1049, 1978

20. Soloway RD, Baggenstoss AH, Schoenfield LJ, et al: Observer error and sampling variability testd in evaluation of hepatitis and cirrhosis by liver biopsy. Am J Dig Dis 16:1082-1086, 1971

Refer to: Oster HA: Obstetric infections. West J Med 134:394-404, May 1981

Obstetric Infections

HENRY A. OSTER, MD, *Ventura, California*

Maternal infections are unique because of their implications for the outcome of pregnancy. Bacterial infections that can be favorably influenced by prompt diagnosis and preventive management include urinary tract infections and chorioamnionitis. However, viral infections such as genital herpes and cytomegalovirus, and the parasitic disease toxoplasmosis, require specialized forms of testing and a complicated management plan.

Altered physiological and immunological states during pregnancy are important in understanding the pathophysiology of maternal infections.

NUMEROUS ADVANCES, particularly in the fields of anaerobic bacteriology and virology, have inspired this review. The reader is referred to the text edited by Charles and Finland[1] for detailed historical information.

Bacterial Diseases

Urinary Tract Infections

Physiological changes occur to a varying extent in the urinary tract of pregnant women from the seventh week of gestation. These changes progress to delivery and resolve by the second postpartum month.[2] Pelvocaliceetasis and dilatation with hypertrophy of the ureters are characteristic in normal pregnancies, with sparing of the pelvic ureter. The ovarian vein syndrome has been postulated to explain the greater incidence of these changes on the right side. Symptomatic ureteral obstruction resulting from compression of the ureter by the right ovarian vein has been confirmed, but the relative contribution of this entity as a cause of hydroureter during pregnancy is still questioned.[2] Hydroureter can be demonstrated in experimental animals given estrogens; however, it is not consistently reproduced in women taking these agents.[3,4] Vesicoureteral reflux may occur intermittently during pregnancy and, therefore, be more common than has been reported.[5]

Although physiological changes are important in understanding the increased incidence of symptomatic urinary tract infections during pregnancy, of greater etiologic significance is the presence of asymptomatic bacteriuria. This generally antedates pregnancy and is detectable in 4 percent to 7 percent of women at their initial prenatal visit.[4,6,7] Bacteriuria is more common in older women (who also tend to be multiparous) and has been correlated with obstetric and perinatal complications.[7,8] Detection of asymptomatic bacteriuria with properly collected, serial quantitative cultures is emphasized.

Antibody-coated bacteria can be detected experimentally by direct fluorescent antibody (FA) techniques. This is considered useful in localizing infections of the renal parenchyma; however, methodology still requires standardization.[9,10] Furthermore, positive FA tests have been reported with hemorrhagic cystitis and are presumed to result from leaking of serum antibody from the bladder mucosa.[10] Harris and co-workers[9] studied

From the Department of Medicine, University of California, Los Angeles, School of Medicine.

Submitted, revised, October 1, 1980.

Reprint requests to: H. A. Oster, MD, 148 Brent Street, Ventura, CA 93003.

ABBREVIATIONS USED IN TEXT

CMV = cytomegalovirus
FA = fluorescent antibody (test)
FTA-ABS = fluorescent treponema antibody absorption (test)
HSV = herpes simplex virus
PPD = purified protein derivative

asymptomatic bacteriuria of pregnancy and noted diminished creatinine clearance in those women with positive FA tests. The FA test was positive in 50 percent of women with bacteriuria and was shown to convert from negative to positive in one patient with recurrent infection. Pyelonephritis subsequently developed in two of the women in both the FA-positive group and the FA-negative group. In patients with positive FA tests or certain circulating antibodies, permanent abnormalities are more likely to be shown on intravenous pyelography. Also, these women are likely to have recurrent bacteriuria, usually due to relapse.[9-11] Relapse is defined as recurrence with the same serotype of *Escherichia coli* or by the same species of organism if other than *E coli*.[12]

Most women will remain free from bacteriuria after a ten-day course of therapy, but should be closely followed for recurrence. Some patients will require a second course of therapy with another agent, depending on the sensitivity of the infecting organism. When repeated recurrences or chronic infections occur, the use of continuous suppressive antibiotic therapy with an agent such as nitrofurantoin is suggested for the remainder of pregnancy (see Figure 1).[13] If reinfection can be established, administration of lower (such as once a day) prophylactic doses of the drug is sufficient. Urologic investigation should be postponed for at least 12 weeks following parturition. Suppressive therapy is also recommended following an episode of pyelonephritis and should be continued until two weeks postpartum.[14]

Sulfisoxazole and ampicillin are also suitable agents for treatment of bacteriuria. Sulfonamides should be avoided during the late stage of pregnancy, and breast feeding should be discontinued if sulfonamides are taken because of potential kernicterus or hemolysis (due to glucose-6-phosphate dehydrogenase deficiency in the infant). Trimethoprim, although effective for therapy and prophylaxis,[12] requires further study to determine the safety of its use during pregnancy.

Studies suggest that perinatal mortality due to urinary tract infections is influenced by metabolic and physiological events occurring in the mother,[7,8,15] Effective management of bacteriuria during pregnancy reduces this risk; however, in approximately 1 percent of women bacteriuria develops later in pregnancy and may be missed by screening cultures.[4,16] Serial urine cultures during the third trimester may be useful in detecting these cases.

The value of chemoprophylaxis in patients with catheters for postpartum urinary retention has been reaffirmed.[17]

Postpartum Infections

Gopelrund and co-workers[18] found that colonization of the cervix with *Escherichia coli* and *Bacteroides fragilis* progressively diminished during gestation and increased sharply postpartum. Colonization with other pathogenic organisms varied to a lesser extent during gestation but also increased by the third postpartum day. Several re-

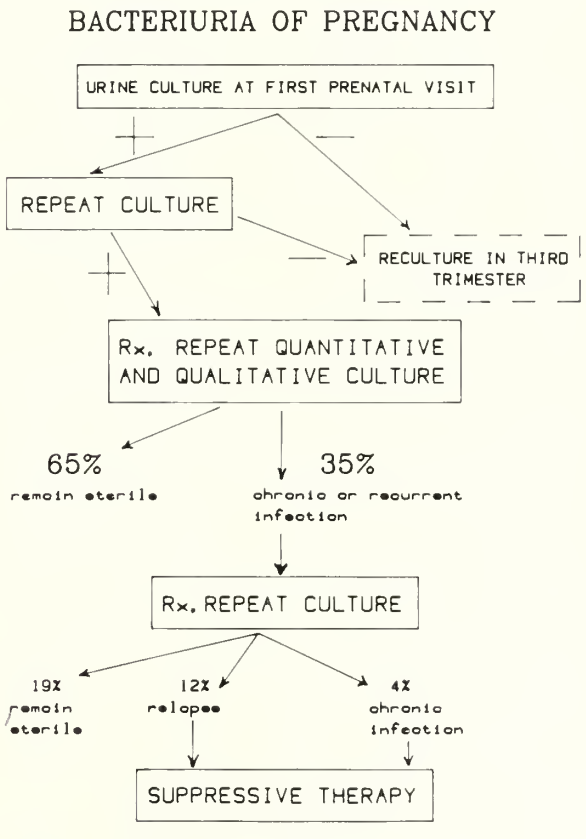


Figure 1.—Bacteriuria of pregnancy. (Adapted from Andriole,[4] Marchant,[6] and Whalley and Cunningham.[13] Graphics courtesy of Ventura County Research Foundation.)

ports involving postpartum infections have underscored the pathogenicity of indigenous flora.[19,20] The effects of prophylactic antibiotic therapy on endometrial flora were studied by Gibbs and Weinstein.[21] Following administration of both clindamycin and gentamicin for only eight hours, decreased colonization with aerobic and anaerobic cocci occurred. However, colonization with *E coli* increased, and the growth rate of enterococci was not significantly changed.

Chorioamnionitis. Chorioamnionitis is a major cause of maternal and perinatal mortality.[22] It is usually an ascending infection associated with premature rupture of the membranes; however, contamination of the amniotic fluid by bacteria may occur with intact membranes and has been associated with bacteriuria.[15] Inhibition of bacterial growth by a factor in amniotic fluid confers protection in the third trimester, but this mechanism may be compromised by the presence of meconium.[23] Many infants whose deliveries have been complicated by chorioamnionitis do not become ill. Additionally, in some newborns only transient bacteremia occurs.[24]

Combined parenteral antibiotic therapy and prompt delivery is advocated in clinically suspected cases.[22]

Septic abortion. Septic abortion is a major cause of bacteremia in general hospitals.[25,26] Anaerobic organisms predominate, and *E coli* is the major aerobic isolate. Bacteremia is polymicrobial in a significant minority of cases. The lack of correlation between results of endometrial cultures and blood cultures illustrates the limited clinical usefulness of cultures from lochial secretions.

Spontaneous septic abortion is much more likely to develop in pregnant women with an intrauterine device in place.[27] Removal of the device is recommended. Barring this, the pregnancy should be managed expectantly and therapeutic abortion may require consideration.

Endometritis. Postpartum endometritis has a reported incidence of only 3.8 percent in a varied population group.[28] The incidence is several times greater following cesarean section. Gibbs and coworkers[20] compared the quantitative frequency of organisms found in the endometria of 27 patients with clinical endometritis with that found in the endometria of 47 patients who had delivered vaginally but who were clinically without infection (Table 1). Nine of the 27 patients with infection had had cesarean sections.

In a survey of female genital tract infections

TABLE 1.—*Postpartum Bacterial Isolates*

	Endometritis†	*Septic Abortion**		*Normal†*
		Percent Isolates		
	Percent Patients	*Blood*	*Endometrium*	*Percent Patients*
Aerobes	..	..	62	..
Escherichia coli	14	13	9	14
Streptococcus				
Group A	7	..	2	..
Group D	18	3	9	8.5
Klebsiella-Enterobacter	3	6	2	2
Proteus	7	..	2	..
Staphylococcus				
aureus	11	3	4	..
epidermidis	25	3	9	17
Diphtheroids	48	..	6	63
Miscellaneous	..‡	6§	..	..¶
Anaerobes	78	61	38	..
Cocci	..	19	15	..
Peptostreptococcus	33	10	8	63
Peptococcus	37	10	7	55
Bacteroides fragilis	7	..	3	10
Bacteroides, other	22	19	8	13
Fusobacterium	..	10.5	2	2
Miscellaneous	..	16‖	..	..

*Finegold et al.[19]
†Gibbs and Weinstein.[21]
‡10%+ for *M hominis* and 85%+ for T mycoplasma.
§*Pseudomonas* and *Haemophilus* (1 each).
‖*Propionibacterium.*
¶15%+ for *M hominis* and 85%+ for T mycoplasma.

involving bacteremia, Ledger and co-workers[29] reported that 86 percent were associated with pregnancy. *E coli* was the predominant aerobic isolate. Anaerobes were recovered in 29 percent, possibly a low estimate because of the techniques employed. Monif and Baer[30] also described polymicrobial bacteremia in 22 percent (13 of 59) of patients with septicemia following vaginal deliveries or cesarean sections. *Corynebacterium vaginale (Haemophilus vaginalis)* was frequently found in their patients.[31]

Thus, there are similarities among the categories of postpartum sepsis, which allow generalizations regarding therapy. Several newer regimens have been advocated for serious postpartum infections.[32-35] Two of these reports involve the use of multiple drugs.[32,33] Cefamandole has been used as a single agent in a group of patients in whom endometritis following cesarean section was the predominant infection.[35] Early favorable experience has been cited for cefoxitin therapy.[34] Further studies are necessary to compare results of initial therapy with these agents to those obtained with drug combinations (such as penicillin, clindamycin and gentamicin), currently recommended as the initial therapy of choice for serious obstetric infections.

Amikacin[36] is useful for serious infections caused by highly resistant Gram-negative rods.

Infections following cesarean section. Prolonged labor and premature rupture of membranes are generally accepted risk factors for infections following cesarean section.[37-39] The pathogenesis involves ascent of organisms into the amniotic fluid which in turn contaminates the operative site.[40] The incidence of infection is directly related to the duration of membrane rupture and increases sharply after six hours. Isolates from amniotic fluid and endometrium are polymicrobial, with a predominance of anaerobes. However, studies have confirmed the effectiveness of prophylaxis with cephalosporins in patients at risk following cesarean section.[37,38] Ampicillin prophylaxis initiated *after* clamping of the cord is also reportedly effective.[39]

Fetal monitoring. An overall increase in maternal infection rates resulting from fetal monitoring has not been demonstrated unequivocally. Fetal scalp infections are rare but may have serious consequences.[41,42] Newer preventive techniques have been studied,[43] but are of dubious value when infection rates are already extremely low as a result of standard practices.

Fetal monitoring is contraindicated in the presence of active genital herpes infection.[44]

Pneumonia

Finland has provided a superb study of pneumonia in pregnancy, detailing an incidence of one case per 1,000 pregnancies in Montreal.[45] The highest incidence of pneumonia occurred during the third trimester, and maternal mortality was highest during the 37th through the 40th week of gestation. Primiparas and those older than 40 years had a higher mortality.

The introduction of antibiotic therapy was followed by a dramatic reduction in maternal mortality from 20 percent to 3.5 percent. Although there were no fetal deaths after the 37th week of gestation, the overall fetal mortality was unchanged with antibiotic therapy.

Pneumonia from all sources during pregnancy still represents a major cause of nonobstetric maternal morbidity and mortality.[46,47] *Streptococcus pneumoniae* and *Mycoplasma pneumoniae* are common causes.[47,48] *Staphylococcus aureus* and *Haemophilus influenzae* are less frequent, but both may also occur as superinfections with influenza.

Leukocytosis is less useful in the differential diagnosis as term approaches. The onset of labor may be accompanied by pronounced leukocytosis, which reverts to normal several days after parturition.[49,50]

The importance of reducing the risk of aspiration during labor and delivery has been emphasized.[51]

Earlier diagnosis and intensive management with emphasis on fetal monitoring may allow further reduction of fetal death rates.

Other Bacterial Infections

Streptococcus. Group B streptococcus causes maternal infections, particularly endometritis[52] as well as meningitis,[53,54] and urinary tract infection.[55] These organisms are able to colonize the maternal genital tract at varying rates and thereby pose a risk to the neonate. There is a high rate of transmission of the organisms (predominantly serotype III) to the respiratory tract of newborns.[56] The early-onset form of disease characterized by sepsis tends to involve infants of complicated deliveries and has a high mortality. It is

caused by organisms of the same serotype (usually Ia or III) as those colonizing the maternal genital tract. The late-onset form occurs after the first postpartum week and usually involves meningitis. It is caused predominantly by serotype III organisms and may be acquired from other sources. Maternal colonization with serotype III organisms apparently stimulates antibody production, which may be of protective benefit to the neonate.[57]

Ampicillin prophylaxis during labor has been shown to reduce colonization in infants of mothers at high risk.[58] However, only a third of women in whom colonization occurs carry the organism chronically in the vagina and, therefore, screening cultures are not generally useful.[59]

Group A streptococci are rarely reported as a cause for puerperal sepsis in this era of antibiotic therapy; however, its epidemic potential should still be recognized.[60]

Necrotizing fascitis may rarely occur following either spontaneous delivery or cesarean section.[61]

Listeria. Listeria produces a variety of illnesses and, in neonates, may mimic either early- or late-onset infection resulting from group B streptococci.[62] Early therapy for maternal listeriosis with penicillin apparently protects the fetus; however, maternal illness may be clinically inapparent.[63]

Pelvic abscess. Pelvic abscess is a rare sequel to therapeutic abortion.[64] Its pathogenesis involves an inapparent perforation of the uterus.

Puerperal mastitis. Studies support the conservative management of isolated cases of puerperal mastitis.[65] The oral administration of an antistaphylococcal agent such as dicloxacillin and continued breast feeding are without ill effects.

Sexually Transmitted Diseases

Condylomata acuminata. Genital warts enlarge during pregnancy and regress following delivery.[66] Neonatal laryngeal papillomas have been associated.[67]

Chlamydiae. Chlamydiae colonize the genitourinary tract in up to 20 percent of women attending prenatal clinics.[68] Genital stains of *Chlamydia trachomatis* have been associated with abnormal pap smears in the mother and conjunctivitis and pneumonia in the neonate.[69] There is a high rate of transmission at parturition; however, intrauterine infection apparently does not occur.[70]

Mycoplasmas. Genital colonization with mycoplasmas, *Mycoplasma hominis* and *Ureaplasma urealyticum* (formerly called T strains of mycoplasma), varies directly with the frequency of sexual exposure. An association with prematurity has been postulated.[71] Ureaplasma colonization has been associated with habitual abortion.[72] Serious maternal infections with *M hominis* have been well described, with recent addition of a case involving septic arthritis.[73] Further study is necessary to define the extent by which mycoplasmas contribute to postpartum febrile illnesses.

Gonorrhea. Gonococcal infections during pregnancy are known to be potentially severe and pose a threat to the fetus and newborn.[74,75] Salpingitis occurs during the first trimester.[76] Culture screening should be carried out in high-risk populations. Therapy for mothers who are allergic to penicillin is problematic, particularly in cases of disseminated infections. Cefoxitin is a promising alternative to erythromycin and has been efficacious against strains producing penicillinase.[77] Spectinomycin is effective for cervicitis.

Syphilis. In risk populations it is advisable to repeat the serological test for syphilis during the third trimester.[78] The fluorescent treponema antibody absorption (FTA-ABS) test has been shown to be reliable for confirmation in those pregnant women who had positive findings on initial screening.[79] Adequate doses of erythromycin are advocated for maternal syphilis in the presence of penicillin allergy.[66]

Herpes simplex. Rare cases of severe maternal dissemination of herpes simplex virus (HSV) are reported.[80,81] However, recent emphasis has been placed on the increasing incidence of genital herpes and its association with neonatal disease. The infant may be inoculated either at the time of vaginal delivery or by an ascending route when the membranes rupture more than four to six hours before delivery. Transplacental infection is rare.[82,83]

Vontver and co-workers[84] reported that 24 percent (7 of 29) of primary genital infections were due to HSV type 1. All of 40 recurrent infections were due to HSV type 2. Visintine and colleagues[83] indicate that approximately 75 percent of virus isolates from infected newborns are HSV type 2.[83] The incidence of infections due to HSV is increased in premature infants.

Papanicolaou smears are useful diagnostically if positive; however, cytologic studies have not been generally reliable.[84,85] Serological testing should be combined with attempts to isolate the virus to document infection with HSV.

Although recurrent maternal infection poses

less overall risk to the infant than does primary infection, the approach at the time of delivery should be similar.[83,86] Kibrick[87] has summarized the indications for cesarean section in women with genital herpes at term as well as infection control guidelines for mother and infant. Clearly, if genital herpetic lesions are present at term and membranes are unruptured, or ruptured for less than six hours, neonatal infection can be prevented. If membranes are ruptured for as long as 24 hours, however, fetal exposure has almost certainly occurred already.

Women who have a history of genital herpes or who give a history of exposure to a sex partner with active herpes should be followed carefully.[88] Viral cultures should be done at appropriate intervals to exclude persistent cervicovaginal shedding of HSV.[84,89] The importance of frequent (weekly) examination of the genitalia is also emphasized.[90] Atypical, erosive lesions should be cultured in the appropriate clinical setting.[91] Newer techniques for rapid viral diagnosis, such as immunofluorescent studies of smears from lesions, are likely to augment the diagnostic yield of viral cultures.

An interesting case report exists of apparent retrotransmission of HVS type 2 from a breast-fed infant to the mother in whom lesions of both breasts developed.[92]

There is no recommended effective therapy for genital herpes.

Trichomonas. Trichomonal infections are more prevalent during pregnancy and the parasite may produce vaginitis in the female neonate as well. Metronidazole therapy should be avoided during pregnancy. If absolutely necessary, this agent should be reserved for the late stages of pregnancy.[66,93] Topical therapy with an agent such as clotrimazole may be effective for less resistant cases of trichomonas.[94]

Mycobacterial Diseases

Tuberculosis

Sensitivity to intermediate-strength, purified protein derivative (PPD) is unchanged during pregnancy. Effective chemotherapy of tuberculosis has removed the risk for the fetus and improved the maternal prognosis comparable to that seen in the absence of pregnancy.[95] The prognosis for extrapulmonary tuberculosis is unchanged as well. Experience with newer agents has been favorable.[96]

Leprosy

A series of 62 cases of maternal leprosy was reported by Maurus.[97] Most cases were managed with sulfone drugs; however, one case was treated with rifampin. Patients with lepromatous and dimorphic conditions showed an increased risk of obstetric complications, but those treated for the tuberculoid type did not. False-positive serological tests for syphilis were frequent.

Viral Diseases

The severity of certain viral infections during pregnancy suggests the possibility of impaired cell-mediated immunity. Although changes in lymphocyte subpopulations have been reported during pregnancy, amounts of T and B lymphocytes are probably not significantly changed.[98,99] Studies have suggested the presence of a serum inhibitory factor affecting phytohemagglutinin-induced lymphocyte transformation and reactivity in mixed lymphocyte cultures.[100,101] A decrease in both immune determinations has been reported for rubella.[102] Rubella hemagglutination inhibition titers have been shown to vary on serial testing during succeeding pregnancies in the same woman, but the significance of this observation is unclear.[103] In contrast, antibody response to influenza vaccine is similar to that of nonpregnant adults.[104] IgG antibody titers may diminish in late pregnancy as a consequence of increased plasma volume.[105]

Cytomegalovirus

Cytomegalovirus (CMV) infection is the most common congenital infection in the United States. Infection as measured by seroconversion increases during adolescence and early adulthood as the virus is passed by way of intimate contact. A third to a half of women remain seronegative for CMV and represent a risk group for acquisition of infection during gestation.[106] If acquired transplacentally in the first trimester, CMV is frequently associated with severe disease in the fetus.[107] Intrauterine infection acquired later in gestation characteristically does not produce clinical illness; however, it may result in developmental defects.[108] Congenital infections have been observed in consecutive pregnancies, indicating that maternal antibodies are not completely protective.[109] However, clinically apparent infection does not occur in infants of healthy mothers who have preexisting antibody.[110,111]

Excretion of cervical virus appears to be sup-

pressed early in pregnancy and may develop in up to 28 percent of women by the third trimester.[112] As in the case of herpes, viral cultures are the most reliable means of establishing that an infection exists. Prolonged or recurrent asymptomatic excretion in urine or cervical secretions is common, particularly during pregnancy.

In a prospective study of 200 mothers, Leinikki and co-workers[110] found that up to 73 percent of women had detectable CMV antibodies early in pregnancy. Seropositivity increased to 82 percent at term. The fluorescent antibody test was more reliable than the complement fixation test. Fluctuations in antibody titers during gestation may have been due to reactivated infections. A very low incidence of maternal virus excretion was noted at term.

Intrauterine infection was present in 2 percent of infants. Perinatal infection, documented by virus excretion, developed in 30 percent. The IgM antibody response was frequently absent in the presence of congenital CMV infection.

Hepatitis

Reports of the severity of hepatitis during pregnancy involve populations whose nutritional status was poor.[106] Hepatitis B is frequently transmitted to the neonate as a result of acute peripartum illness and may also be acquired from chronic carrier mothers. The great majority of cases of neonatal hepatitis are presumably acquired by direct exposure to infectious secretions during delivery. The most important factors in neonatal transmission appear to be the presence of the e antigen in the mother's serum and the absence of the anti-e antibody.[113]

Immune serum globulin has failed to prevent hepatitis B in neonates.[114] Administration of hepatitis B immune globulin in repeated doses may prove useful for this purpose.[115]

Neither hepatitis A nor hepatitis B has been associated with congenital defects.[106]

Varicella-Zoster Virus

Varicella is uncommon during pregnancy because most persons acquire the illness in childhood and are therefore immune. Pregnant women are at equal risk for contracting varicella as the population at large, but the illness tends to be more severe.[116]

Congenital defects are rarely reported; however, zoster immune globulin may be considered in susceptible gravidas exposed to varicella.[106] Zoster immune globulin should be used for prophylaxis of the newborn if maternal illness develops during the interval from five days before to two days after birth. There are reports of herpes zoster in newborns which may have been secondary to virus exposure in utero, but documentation is lacking.[117]

Enteroviruses

Enteroviruses may produce severe disease in neonates. Serious transplacental infection with coxsackie B_2 virus has been suggested.[118] Maternal coxsackie B_3 and B_4 infections have been linked with congenital heart disease.[119] The most common defect reported is tetralogy of Fallot (in contrast to patent ductus arteriosus or pulmonary stenosis noted in congenital rubella). However, reliable evidence implicating these defects is lacking.

Echovirus type 11 was described as occurring in the 39th week of gestation and resulted in stillbirth.[120] Virus was not isolated from the fetus. Although echovirus may cross the placenta, it is not associated with congenital defects.[119]

Erythema Infectiosum

There was no increase in pregnancy complication rates following an epidemic of erythema infectiosum in England.[121] This information supports the apparent lack of teratogenicity associated with this illness.

Fungal Diseases

Candida

The incidence of cervical colonization with *Candida* increases with duration of gestation.[18] *Candida* vulvovaginitis occurs more frequently in pregnancy and has a higher relapse rate. Miconazole or clotrimazole may offer a therapeutic advantage over nystatin.[122,123] Significant candiduria may occur associated with diabetes or following antibiotic therapy. This requires further investigation if colony counts are persistently above 10,000 organisms per ml of urine.[124]

Systemic Mycoses

Coccidioidomycosis is a major cause of maternal mortality in highly endemic areas of the southwestern United States. Transplacental infection is apparently possible;[125] however, the

placenta may be involved in the absence of fetal infection.[126]

Cryptococcosis occurs rarely during pregnancy. Involvement of the fetus in several untreated cases has not been described.[127]

Coccidioidomycosis, cryptococcosis and blastomycosis[128] have been treated during pregnancy with amphotericin B. Combined therapy with this agent and flucytosine for cryptococcal meningitis, although possibly advantageous, has not yet been tested in pregnant women.[129]

Parasitic Diseases

Toxoplasmosis

Desmonts and Remington[130] have provided a comprehensive account of maternal toxoplasmosis. Approximately 75 percent of women in the United States lack antibodies to *Toxoplasma* organisms and are at risk for maternal infection, which is characteristically a minor illness. Infection acquired at the time of conception has uncertain effects. In a study of French women, the risk of transmission to the fetus varied from approximately 17 percent during the first trimester to 59 percent in the third. However, the chance of severe or symptomatic infection was 80 percent for those infected in the first trimester and decreased to only 8 percent for those infected in the third trimester.

Stray-Pederson and Lorentzen-Styr[131] reported that 12.6 percent of young Norwegian women are seropositive, using the dye test. This test was more sensitive than the IgG indirect fluorescent antibody test. The seroconversion rates during pregnancy were 0.2 percent.[105] A transmission rate of 46 percent and an incidence of congenital infection approaching 1 per 1,000 was also reported.[105]

These investigators again studied endometrial biopsies of women who had recurrent spontaneous abortion.[132] Tachyzoites were detected in tissue from persons with negative serological findings; however, the organism could not be isolated from the specimens by animal inoculations. The possibility of sexual transmission of *Toxoplasma* organisms was not suggested in their study.

IgM indirect FA testing is useful in detecting recent infections. Maternal infection with risk for the fetus is probable when two of the three following criteria are present: (1) clinically suggestive illness, (2) dye test titer of 1:1,000 or greater and the presence of IgM antibody titer of 1:80 or greater (after the second month) or (3) a rising titer after the second month (dye tests should be confirmed with IgM indirect FA test). A dye test titer of 1:1,000 or greater within two months of conception indicates that infection occurred before conception with minimal risk for the fetus.

Therapy with pyrimethamine and sulfadiazine may be of value, but the former agent is potentially teratogenic.[130] Hygienic practices are advised in households inhabited by cats.

Malaria

Malaria in pregnancy is associated with higher than expected rates of parasitemia.[133] Transplacental infection occurs rarely with all four species of *Plasmodium*.[134] Concentration of parasites within the placenta was noted in 16 percent of African women even though only 5.6 percent were parasitemic at the time.[133] Parasitemia was noted in only 0.2 percent of newborns. The absence of maternal IgG antibody specific for *Plasmodium* organisms may allow for higher rates of neonatal acquisition among those native to malaria-free areas of the world.

A recent report in the British literature details the therapy of a patient in her seventh month of gestation who had vivax malaria.[135] Chloroquine and primaquine were administered during gestation, and healthy twins were delivered at the 39th week.

The use of pyrimethamine-sulfadoxine (Fansidar) for prophylaxis is contraindicated during pregnancy. Travelers should be advised regarding the risks in areas endemic for chloroquine-resistant strains of *P falciparum*. Chloroquine remains the most suitable agent for therapy and prophylaxis of sensitive strains.

Primaquine is not generally required for prophylaxis of malaria unless heavy exposure to *P vivax* or *P ovale* occurs in rural areas. This drug is necessary for therapy with these plasmodia; however, it should be withheld, whenever possible, until after parturition.[136]

Amebiasis

Amebiasis is a frequent condition associated with maternal mortality in underdeveloped countries such as Tanzania.[137] Factors unique to such a population (such as malnutrition) probably play a role in prognosis. Dehydroemetine dihydrochloride may be necessary for tissue-based infections, such as amebic abscess or dysentery, during

the first trimester when metronidazole is contraindicated. Chloroquine is useful in therapy of liver abscess.

Discussion

The value of preventive management of maternal infections is illustrated by the approach to asymptomatic bacteriuria of pregnancy. Screening cultures done at the first prenatal visit provide the basis for the approach to this problem. A comprehensive management plan should be undertaken in those women with recurrent or chronic infections.

Several newer antimicrobial agents are relatively safe and effective when taken during pregnancy. However, trimethoprim and metronidazole should be administered with reservation until more is known of their possible effects on the fetus.

The use of combined antibiotic therapy for serious postpartum sepsis is indicated by studies demonstrating pathogenicity of a variety of anaerobic and acrobic flora indigenous to the female genital tract. Antibiotic prophylaxis effective for Gram-positive cocci and *E coli* is advantageous in patients at high risk who are undergoing cesarean sections. The value of antibiotic prophylaxis in a woman during childbirth who is at risk for bacterial endocarditis has been proposed but has not been established.[145] Serum levels following an equivalent dose of antibiotic drugs such as ampicillin and cephradine are lower than expected during pregnancy.[139]

Epidemiologic studies have shown the varied incidence of diseases such as cytomegalovirus, hepatitis B and toxoplasmosis in different populations. In countries where serological conversion rates are low, the risk for symptomatic congenital infection is correspondingly high. Further study of the transmissibility of diseases such as herpes simplex and toxoplasmosis is vital for the prevention of fetal morbidity and mortality. The value of vaccination for the prevention of cytomegalovirus infection of the fetus is under study. Investigation is complicated by the potential for this virus to assume a latent state and by the unresolved question of oncogenicity, which has been postulated for several DNA viruses.

Altered maternal immune mechanisms considered together with the observations on the propensity of latent DNA viruses to reactivate during pregnancy provide topics for future study.

REFERENCES

1. Charles D, Finland M: Obstetric and Perinatal Infections. Philadelphia, Lea & Febiger, 1973

2. Meares EM: Urologic surgery during pregnancy. Clin Obstet Gynecol 21:907-920, 1978

3. Marchant DJ: Effects of pregnancy and progestational agents on the urinary tract. Am J Obstet Gynecol 112:487-501, 1972

4. Andriole VT: Urinary tract infections in pregnancy. Urol Clin North Am 2:485-498, 1975

5. Mattingly RF, Borkowf HI: Clinical implications of ureteral reflux in pregnancy. Clin Obstet Gynecol 21:863-873, 1978

6. Marchant DJ: Urinary tract infections in pregnancy. Clin Obstet Gynecol 21:921-929, 1978

7. Williams JD, Reeves DS, Condie AP, et al: Significance of bacteriuria in pregnancy, *In* Kass EH, Brumfitt W (Eds): Infections of the Urinary Tract. Chicago, The University of Chicago Press, 1975, pp 8-18

8. Sever JL, Ellenberg JH, Edmonds D: Urinary tract infections during pregnancy: Maternal and pediatric findings, *In* Kass EH, Brumfitt W (Eds): Infections of the Urinary Tract. Chicago, The University of Chicago Press, 1975, pp 19-21

9. Harris RE, Thomas VL, Shelkov A: Asymptomatic bacteriuria in pregnancy: Antibody-coated bacteria, renal function, and intrauterine growth retardation. Am J Obstet Gynecol 126:20-25, 1976

10. Rumans LW, Vosti KL: The relationship of antibody-coated bacteria to clinical syndromes. Arch Intern Med 138:1077-1081, 1978

11. Hanson LA, Ahlstedt S, Goldblum RM, et al: Immunology of urinary tract infections, *In* Kass EH, Brumfitt W (Eds): Infections of the Urinary Tract. Chicago, The University of Chicago Press, 1975, pp 105-113

12. Stamm WE, Counts GW, Wagner KF, et al: Anti-microbial prophylaxis of recurrent urinary tract infections—A double blind, placebo-controlled trial. Ann Intern Med 82:770-775, 1980

13. Whalley PG, Cunningham FG: Short term versus continuous antimicrobial therapy for asymptomatic bacteriuria in pregnancy. Obstet Gynecol 49:262-265, 1977

14. Harris RE, Gilstrap LC 3d: Prevention of recurrent pyelonephritis during pregnancy. Obstet Gynecol 44:637-641, 1974

15. Naeye L: Causes of the excessive rates of perinatal mortality and prematurity in pregnancies complicated by maternal urinary tract infections. N Engl J Med 300:819-823, 1979

16. Harris RE: The significance of eradicating bacteriuria during pregnancy. Obstet Gynecol 53:71-73, 1979

17. Harris RE: Postpartum urinary retention: Role of antimicrobial therapy. Am J Obstet Gynecol 133:174-175, 1979

18. Gopelrund CP, Ohm MJ, Galask RP: Aerobic and anaerobic flora of the cervix during pregnancy and puerperium. Am J Obstet Gynecol 126:858-868, 1976

19. Finegold SM, Bartlett JG, Chow AW, et al: Management of anaerobic infections. Ann Intern Med 83:375-389, 1975

20. Gibbs RS, Odell TN, MacGregor RR, et al: Puerperal endometritis: A prospective microbiologic study. Am J Obstet Gynecol 121:919-925, 1975

21. Gibbs RS, Weinstein AJ: Bacteriologic effects of prophylactic antibiotics in cesarean section. Am J Obstet Gynecol 126: 226-229, 1976

22. Gibbs RS, Castillo MS, Rodgers PJ: Management of acute chorioamnionitis. Am J Obstet Gynecol 136:709-713, 1980

23. Larsen B, Cheng HF, Galask RP: Bacterial growth inhibition by amniotic fluid: VIII. Evaluation of a radiometric bioassay for rapid, in vitro demonstration of phosphate-sensitive bacterial growth inhibitor in amniotic fluid. Am J Obstet Gynecol 135:14-21, 1979

24. Chow AW, Leake RD, Yamauchi T, et al: The significance of anaerobes in neonatal bacteremia: Analysis of 23 cases and review of the literature. Pediatrics 54:736-745, 1974

25. Chow AW, Marshall JR, Guze LB: Anaerobic infections of the female genital tract: Prospects and perspectives. Obstet Gynecol Surv 30:477-494, 1975

26. Chow AW, Guze LB: Bacteriodaceae bacteremia: Clinical experience with 112 patients. Medicine (Baltimore) 53:93-126, 1974

27. Cates W Jr, Ory HW, Rochat RW, et al: The intrauterine device and deaths from spontaneous abortions. N Engl J Med 295:1155-1159, 1976

28. Sweet RL, Ledger WJ: Puerperal infections morbidity—A two-year review. Am J Obstet Gynecol 117:1093-1100, 1973

29. Ledger WJ, Norman M, Gee C, et al: Bacteremia on an obstetric-gynecologic service. Am J Obstet Gynecol 121:205-212, 1975

30. Monif GR, Baer H: Polymicrobial bacteremia in obstetric patients. Obstet Gynecol 48:167-169, 1976

31. Monif GR, Baer H: *Haemophilus (Corynebacterium) vaginalis* septicemia. Am J Obstet Gynecol 120:1041-1045, 1974

32. Ledger WJ, Gee CL, Lewis WP, et al: Comparison of clindamycin and chloramphenicol in treatment of serious infections of the female genital tract. J Infect Dis 135(Suppl):S30-S34, 1977

33. Swenson RM, Lorber B: Clindamycin and carbenicillin in treatment of patients with intraabdominal and female genital tract infections. J Infect Dis 135(Suppl):S40-S45, 1977

34. Ledger WJ, Smith D: Cefoxitin in obstetric and gynecologic infections. Rev Infect Dis 1:199-201, 1979

35. Cunningham FG, Gilstrap LC 3d, Kappus SS: Treatment of obstetric and gynecologic infections with cefamandole. Am J Obstet Gynecol 133:602-610, 1979

36. Mazzei T, Paradiso M, Nicoletti I, et al: Amikacin in obstetric, gynecologic and neonatal infections: Laboratory and clinical studies. J Infect Dis 134(Suppl):S374-S379, 1976

37. Kreutner AK, Del Bene VE, Delamar D, et al: Perioperative cephalosporin prophylaxis in cesarean section: Effect on endometritis in the high-risk patient. Am J Obstet Gynecol 134: 925-935, 1979

38. Phelan JP, Pruyn SC: Prophylactic antibiotics in cesarean section: A double blind study of cefazolin. Am J Obstet Gynecol 133:474-478, 1979

39. Gordon HR, Phelps D, Blanchard K: Prophylactic cesarean section antibiotics: Maternal and neonatal morbidity before or after cord clamping. Obstet Gynecol 53:151-156, 1979

40. Gilstrap LC 3d, Cunningham FG: The bacterial pathogenesis of infection following cesarean section. Obstet Gynecol 53:545-549, 1979

41. Turbeville DF, Heath RE, Bowen FW, et al: Complications of fetal scalp electrodes. Am J Obstet Gynecol 122:530-531, 1975

42. Overturf GD, Balfour G: Osteomyelitis and sepsis: Severe complication of fetal monitoring. Pediatrics 55:244-247, 1975

43. Saling E: A new method to decrease the risk of intrapartum infection. J Perinatal Med 6:206-212, 1978

44. Visintine AM, Nahmias AJ, Josey WE: Genital herpes. Perinatal Care 2:32-41, 1978

45. Finland M: Pneumonia, *In* Charles D, Finland M (Eds): Obstetric and Perinatal Infections. Philadelphia, Lea & Febiger, 1973, pp 167-178

46. Griffith ER: Viral pneumonia in pregnancy: Report of a case complicated by disseminated intravascular coagulation and acute renal failure. Am J Obstet Gynecol 120:201-202, 1974

47. Giesler CF, Webster JR: Pulmonary disease in pregnancy, *In* Sciarra JJ, Depp R (Eds): Gynecology and Obstetrics, Vol 3. Hagerstown, Harper and Row, 1979, pp 1-17

48. Schoenbaum SC, Weinstein L: Respiratory infection in pregnancy. Clin Obstet Gynecol 22:293-300, 1979

49. Wintrobe MM, Lee GR, Boggs DR, et al (Eds): Granulocytes and Monocytes. In Clinical Hematology. Philadelphia, Lea & Febiger, 1974, pp 221-285

50. Ezeilo GG, Wacha D: Pregnancy-induced leucocytosis in Africans, Asians and Europeans. Br J Obstet Gynaecol 84:944-947, Dec 1977

51. Roberts RB, Shirley MA: The obstetrician's role in reducing the risk of aspiration pneumonitis. Am J Obstet Gynecol 124: 611-617, 1976

52. Bayer AS, Chow AW, Anthony BF, et al: Serious infections in adults due to group B streptococci: Clinical and serotypic characterization. Am J Med 61:498-503, 1976

53. Grossman J, Tompkins RL: Group B beta-hemolytic streptococcal meningitis in mother and infant. N Engl J Med 290: 387-388, 1974

54. Wolstan BJ: Group B streptococcal meningitis in adults. Minn Med 56:631-632, 1973

55. Mead PJ, Harris RE: The incidence of group B beta hemolytic streptococcus in antepartum urinary tract infections. Obstet Gynecol 51:412-414, 1978

56. Yow MD, Leeds LJ, Thompson PK, et al: The natural history of group B streptococcal colonization in the pregnant woman and her offspring—I. Colonization studies. Am J Obstet Gynecol 137:34-38, 1980

57. Baker C, Webb BJ, Kasper DL, et al: The natural history of group B streptococcal colonization in the pregnant woman and her offspring—II. Determination of serum antibody to capsular polysaccharide from type III, group B streptococcus. Am J Obstet Gynecol 137:39-42, 1980

58. Yow MD, Leeds LJ, Thompson PK, et al: Ampicillin prevents intrapartum transmission of group B streptococcus. JAMA 241:1245-1247, 1979

59. Anthony BF, Okada DM, Hobel CJ: Epidemiology of group B streptococcus: Longitudinal observations during pregnancy. J Infect Dis 137:524-530, 1978

60. Ogden E, Amstey MS: Puerperal infection due to group A beta hemolytic streptococcus. Obstet Gynecol 52:53-55, 1978

61. Golde S, Ledger WT: Necrotizing fasciitis in postpartum patients. Obstet Gynecol 50:670-673, 1977

62. Halliday HL, Hirata T: Perinatal listeriosis—A review of 12 patients. Am J Obstet Gynecol 133:405-410, 1979

63. Zervoudakis IA, Cederqvist LL: Effect of Listeria monocytogenes septicemia during pregnancy on the offspring. Am J Obstet Gynecol 129:465-467, 1977

64. Gassner CB, Ballard CA: Pelvic abscess. Obstet Gynecol 48:716-717, 1978

65. Nicbyl JR, Spence MR, Parmley TH: Sporadic (nonepidemic) puerperal mastitis. J Reprod Med 20:97-100, 1978

66. McCormack WM: Management of sexually transmissible infections during pregnancy. Clin Obstet Gynecol 18:57-71, 1975

67. Cook TA, Cohn AM, Brunschwig JP, et al: Wart viruses and laryngeal papillomas. Lancet 1:782, 1973

68. Lumicao GG, Heggie AD: Chlamydial infections. Pediatr Clin North Am 26:269-282, 1979

69. Carr MC, Hanna L, Jawetz E: Chlamydiae, cervicitis, and abnormal Papanicolaou smears. Obstet Gynecol 53:27-30, 1979

70. Frommell GT, Rothenberg R, Wang S, et al: Chlamydial infection of mothers and their infants. J Pediatr 95:28-32, 1979

71. Kass EH: The role of unsuspected infection in the etiology of prematurity. Clin Obstet Gynecol 16:134-152, 1973

72. Stray-Pedersen B, Eng J, Reikvam RM: Uterine T-mycoplasma colonization in reproductive failure. Am J Obstet Gynecol 130:307,-311 1978

73. Verinder DG: Septic arthritis due to *Mycoplasma hominis*. J Bone Joint Surg 60-B:224, 1978

74. Rothbard MJ, Gregory T, Salerno L: Intrapartum gonococcal amnionitis. Am J Obstet Gynecol 121:565-566, 1975

75. Genandry RR, Thompson BH, Niebyl JR: Gonococcal salpingitis in pregnancy. Am J Obstet Gynecol 126:512-513, Oct 15, 1976

76. Mehta A, Wright TA: Gonococcal arthritis in pregnancy. Can Med Assoc J 117:1190-1191, 1977

77. Berg SW, Kilpatrick ME, Harrison WO, et al: Cefoxitin as a single-dose treatment for urethritis caused by penicillinase-producing *Neisseria gonorrhaeae*. N Engl J Med 301:509-511, 1979

78. Monif GR, Williams BR, Shuman ST, et al: The problem of maternal syphilis after serologic surveillance during pregnancy. Am J Obstet Gynecol 117:268-270, 1973

79. Manikowska-Lesinska W, Linda B, Zajac W: Specificity of the FTA-ABS and TPHA tests during pregnancy. Br J Vener Dis 54:295-298, 1978

80. Roman-Campos G, Navarro de Roman LI, Toro G: Herpes encephalitis in pregnancy. Am J Obstet Gynecol 135:158-159, 1979

81. Hensleigh PA, Glover DB, Cannon M: Systemic *Herpesvirus hominis* in pregnancy. J Reprod Med 22:171-176, 1979

82. Von Herzen JL, Benirschke K: Unsuspected disseminated herpes simplex infection in a new born. Obstet Gynecol 50:728-730, 1977

83. Visintine A, Nahmias A, Whitley R, et al: The natural history and epidemiology of neonatal herpes simplex virus infections. Presented at International Conference on Human Herpesviruses. Atlanta, Mar 17-21, 1980

84. Vontver LA, Reeves RH, Rattray M, et al: Clinical course and diagnosis of genital herpes simplex virus infection and evaluation of topical surfactant therapy. Am J Obstet Gynecol 133:548-554, 1979

85. Block BSB, Goodner DM: False positive amniotic fluid cytology in a parturient with active genital herpes infection at term. Obstet Gynecol 54:658-660, 1979

86. Amstey MS, Monif GR, Nahmias A, et al: Cesarean section and genital herpes virus infection. Obstet Gynecol 53:641-642, 1979

87. Kibrick S: Herpes simplex infection at term: What to do with mother, newborn, and nursery personnel. JAMA 243:157-160, 1980

88. Spence MR: Inapparent sexual transmission of herpes simplex virus type 2 infection with neonatal death: Case report. Am J Obstet Gynecol 130:590-591, 1978

89. Adam E, Kaufman RH, Mirkovic RR, et al: Persistence of virus shedding in asymptomatic women after recovery from herpes genitalis. Obstet Gynecol 54:171-173, 1979

90. Tejani N, Klein SW, Kaplan M: Subclinical herpes simplex genitalis infections in the perinatal period. Am J Obstet Gynecol 135:547, 1979

91. Young AW, Frankel M, Menegus M: Papular (erosive) herpes genitalis—A clinical variant in sarcoid and pregnancy. Obstet Gynecol 50:730-732, 1977

92. Quinn PT, Lofberg JV: Maternal herpetic breast infection: Another hazard of neonatal herpes simplex. Med J Aust 2:411-412, 1978

93. Morgan H: Metronidazole treatment in pregnancy. Int J Gynecol Obstet 15:501-502, 1978

94. Cave VG, Nikitas J: Gynecologic infection—Other sexually transmissible diseases, *In* Sciarra JJ, Depp R (Eds): Gynecology and Obstetrics, Vol 1. Hagerstown, Harper & Row, 1979, pp 1-16

95. Weinstein L, Murphy T: The management of tuberculosis during pregnancy. Clin Perinatol 1:395-405, 1974

96. Wilson EZ, Thelin TJ, Dilts PV: Tuberculosis complicated by pregnancy. Am J Obstet Gynecol 115:526-529, 1973

97. Maurus JN: Hansen's disease in pregnancy. Obstet Gynecol 52:22-25, 1978

98. Dodson MG, Facog RH, Kerman CL, et al: T and B cells in pregnancy. Obstet Gynecol 49:299-302, 1977

99. Cornfield DB, Jencks J, Binder A, et al: T and B cells in pregnancy. Obstet Gynecol 53:203-206, 1979

100. Saint Hill CA, Finn R, Denye V: Depression of cellular immunity in pregnancy due to a serum factor. Br Med J 3:513-514, 1973

101. Kasakura S: A factor in maternal plasma during pregnancy that suppresses the reactivity of mixed leukocyte cultures. J Immunol 107:1296-1301, 1971

102. Thong YH, Steele RW, Vincent MM, et al: Impaired cell mediated immunity to rubella virus during pregnancy. N Engl J Med 289:604-606, 1973

103. Hall JA, Wills ER, Hall K, et al: Positive rubella titers in pregnancy: A question of validity. Obstet Gynecol 54:235-236, 1979

104. Sumaya CV, Gibbs RS: Immunization of pregnant women with influenza A/New Jersey/76 virus vaccine: Reactogenicity and immunogenicity in mother and infant. J Infect Dis 140:141-146, 1979

105. Stray-Pedersen B: A prospective study of acquired toxoplasmosis among 8,043 pregnant women in the Oslo area. Am J Obstet Gynecol 136:399-406, 1980

106. Waterson AP: Virus infections (other than rubella) during pregnancy. Br Med J 2:564-566, 1979

107. French ML, Thompson JF, White A: Cytomegalovirus viremia with transmission from mother to fetus. Ann Intern Med 86:748-749, 1977

108. Starr SE: Cytomegalovirus. Pediatr Clin North Am 26: 283-293, 1979

109. Stagno S, Reynolds DW, Huang ES, et al: Congenital cytomegalovirus infection: Occurrence in an immune population. N Engl J Med 296:1254-1258, 1977

110. Leinikki P, Granstrom M, Santavuori P, et al: Epidemiology of cytomegalovirus infections during pregnancy and infancy—A prospective study. Scand J Infect Dis 10:165-171, 1978

111. Hayes K, Symington G, Mackay IR: Maternal immunosuppression and cytomegalovirus infection of the fetus. Aust N Z J Med 9:430-433, 1979

112. Hanshaw JB: Cytomegalovirus, *In* Remington JS, Klein JO (Eds): Infectious Diseases of the Fetus and Newborn Infant. Philadelphia, WB Saunders Co, 1976, pp 107-155

113. Yanagida M, Horiguchi S, Fujii T, et al: Failure of maternofetal transmission for small as well as large molecular hepatitis B e antigen. J Pediatr 95:76-77, 1979

114. Tong MJ, McPeak CM, Thursby MW, et al: Failure of immune serum globulin to prevent hepatitis B infection in infants born to HB_sAg positive mothers. Gastroenterology 76:535-539, 1979

115. Reesink HW, Reerink-Brongers EE, Lafeber-Schut BJ, et al: Prevention of chronic HB_sAg carrier state in infants of HB_sAg-positive mothers by hepatitis B immunoglobulin. Lancet 2:436-438, 1979

116. Duong CM, Munns RE: Varicella pneumonia during pregnancy. J Fam Pract 8:277-280, 1979

117. Brazin SA, Simkovich JW, Johnson WT: Herpes zoster during pregnancy. Obstet Gynecol 53:175-181, 1979

118. Richardson J: Suspected transplacental coxsackie infection. Lancet 2:877-878, 1979

119. Hanshaw JB, Dudgeon JA: Enteroviral infections, *In* Major Problems in Clinical Pediatrics, Vol 17. Philadelphia, WB Saunders Co, 1978, pp 182-191

120. Freedman PS: ECHO 11 infection and intrauterine death. Lancet 1:96-97, 1979

121. Cramp HE, Armstrong BD: Erythema infectiosum: No evidence of teratogenicity (Letter). Br Med J 1:1031, 1977

122. Robertson WH: Vulvovaginal candidiasis treated with clotrimazole cream in 7 days compared with 14 day treatment with miconazole cream. Am J Obstet Gynecol 132:321-323, 1978

123. Haram K, Digranes A: Vulvovaginal candidiasis in pregnancy treated with clotrimazole. Acta Obstet Gynecol Scand 57: 453-455, 1978

124. Goldberg PK, Kozinn PJ, Wise GT, et al: Incidence and significance of candiduria. JAMA 241:582-584, 1979

125. Smale LE, Waechter KG: Dissemination of coccidioidomycosis in pregnancy. Am J Obstet Gynecol 107:356-361, Jun 1970

126. McCaffree MA, Altshuler G, Benirschke K: Placental coccidioidomycosis without fetal disease. Arch Pathol Lab Med 102: 512-514, 1978

127. Silberfarb PM, Sarosi GA, Tosh FE: Cryptococcosis and pregnancy. Am J Obstet Gynecol 112:714-720, 1972

128. Neiberg AD, Mavromatis F, Dyke J, et al: *Blastomyces dermatitidis* treated during pregnancy: Report of a case. Am J Obstet Gynecol 128:911-912, 1977

129. Bennett JE, Dismukes WE, Duma RJ, et al: A comparison of amphotericin B alone and combined with flucytosine in the treatment of cryptococcal meningitis. N Engl J Med 301:126-131, 1979

130. Desmonts G, Remington JS: Toxoplasmosis, *In* Remington JS, Klein JO (Eds): Infectious Diseases of the Fetus and Newborn Infant. Philadelphia, WB Saunders, 1976, pp 191-332

131. Stray-Pedersen B, Lorentzen-Styr AM: The prevalence of toxoplasma antibodies among 11,736 pregnant women in Norway. Scand J Infect Dis 11:159-165, 1979

132. Stray-Pedersen B, Lorentzen-Styr AM: Uterine toxoplasma infections and repeated abortions. Am J Obstet Gynecol 128:716-721, 1977

133. Taufa T: Malaria in pregnancy. Papua N G Med J 21: 197-206, 1978

134. Lee RV: Parasitic infections, *In* Burrow GN, Ferris TF (Eds): Medical Complications During Pregnancy. Philadelphia, WB Saunders Co, 1975, pp 438-463

135. Smith AM: Malaria in pregnancy. Br Med J 4:793, 1972

136. Chemoprophylaxis of malaria. Morbid Mortal Weekly Rep 27(Suppl):81-90, 1978

137. Armon PJ: Amoebiasis in pregnancy and the puerperium. Br J Obstet Gynaecol 85:264-269, 1978

138. Polk BF, Schoenbaum SC: Prophylactic antibiotics in obstetrics. Clin Obstet Gynecol 22:379-384, 1979

139. Philpson A, Stiernstedt G: Pharmacokinetics of cephradine in pregnancy, *In* Nelson JD, Grassi C (Eds): Current chemotherapy and infectious disease, Vol 2. Washington DC, American Society for Microbiology, 1980, pp 1172-1174

Refer to: Bennett RM: Fibrositis: Misnomer for a common rheumatic disorder (Medical Progress). West J Med 134: 405-413, May 1981

Fibrositis: Misnomer for a Common Rheumatic Disorder

ROBERT M. BENNETT, MD, *Portland*

Fibrositis is a misnomer for a very common form of nonarticular rheumatism. The name implies an inflammatory process in fibroconnective tissue which has never been verified. The symptoms of fibrositis are ill-defined musculoskeletal pain made worse by stress, cold, noise and unaccustomed exercise; there is usually a significant element of depression, nonrestorative sleep, chronic fatigue and early morning stiffness. Results of physical examination are strikingly normal, apart from painful tender spots which are remarkably consistent in location from patient to patient. It is important to realize that fibrositis can complicate diseases such as rheumatoid arthritis and systemic lupus erythematosus, where its prompt recognition is essential in averting inappropriate medication. Drug therapy alone is seldom effective in alleviating symptoms; a carefully planned education program is necessary to readjust both psyche and soma.

FIBROSITIS is generally used to describe a type of nonarticular rheumatism characterized by aching and stiffness in the presence of focal tender points.[1,2] It is a poorly defined and controversial term that implies some knowledge of a specific underlying pathological conditon (that is, inflammation of fibroconnective tissue) which has never been proved to exist. The absence of a well-defined pathological lesion, normal laboratory test results and an apparently inappropriate degree of pain and misery have led many physicians to regard this condition as purely psychogenic in origin or a form of malingering. This reluctance to make a diagnosis of fibrositis has led to the use of other terms (Table 1) or the elaboration of nonscientific explanations for this symptom complex. *Fibrositis* as now generally used is descriptive of a common clinical syndrome without any implication as to pathogenesis. Recent clinical studies have led to a sharper definition of fibrositis. The rapidly expanding areas of sleep research, neurotransmission and pain perception have provided some intriguing clues which may be germane to the symptom complex of fibrositis. The purpose of this review is to present these

From the Section of Rheumatology, Department of Medicine, University of Oregon Health Sciences Center, Portland.

This work is supported in part by a Clinical Research Center Grant, the Arthritis Foundation and by a grant from the Oregon Chapter of the Arthritis Foundation.

Reprint requests to: Robert M. Bennett, MD, Head, Rheumatology Section, Department of Medicine, University of Oregon Health Sciences Center, Portland, OR 97201.

TABLE 1.—*Terminology of Fibrositis*

Fibrositis	Myofasciitis
Fibromyositis	Myositis
Myofascial pain syndrome	Strain
Muscular rheumatism	Sprain
Fasciitis	Trigger point
Myalgia	Psychogenic rheumatism
Nonrestorative sleep syndrome	Pain amplification syndrome

newer ideas and, it is hoped, stimulate a heightened awareness and more scientific approach to this common medical problem.

Historical Aspects

The term fibrositis was coined by Gowers in 1904 in a paper in the *British Medical Journal* on lumbago that also mentioned fibrositis of the arm.[3] He hypothesized that both conditions were due to inflammation of the fibrous tissue of muscle; no pathological verification was provided. In the same year Stockman reported findings from seven biopsy studies of "fibrositic nodules" in a group of patients complaining of stiffness, aching and painful muscular movement.[4] The nodules that were excised showed a low-grade inflammatory reaction which he ascribed to "small colonies of microbes invading the tissues and causing a reaction which comparatively rapidly destroys the invader." However, his cultures remained sterile. Subsequent workers, such as Abel, Sibert and Earp from St. Louis, Missouri,[5] and Collins[6] and Slocumb[7] both from the Mayo Clinic, have failed to find any evidence of a low-grade inflammatory response in biopsy specimens of muscle.

The concept of fibrositis was popularized by Llewellyn and Jones of Bath, England, in a book published in 1915 entitled *Fibrositis*.[8] They defined myofibrositis as "inflammatory change in the interstitial fibrous tissues of a striated or voluntary muscle." Stockman further reinforced this unfounded concept in a chapter in his own book *Rheumatism and Arthritis*.[9] A different view was taken by Elliott in 1944.[10] On the basis of electromyographic studies he suggested that fibrositic nodules were the result of localized muscle spasm. Further support of the muscle spasm concept was provided by the studies of Kelly, who showed that there was a temporary relief of symptoms in 30 percent to 40 percent of cases after the use of local procaine injections into the primary myalgic spot, rather than the area of referred pain.[11] This he attributed to an interruption of a reflex arc. At about the same time Copeman and Ackerman published two convincing studies which indicated that fat herniation and pediculation through adjacent fascial planes were responsible for the painful "trigger points."[12,13] In 1968 Kraft, Johnson and LaBan defined the "fibrositis syndrome" as having four essential features: point tenderness of muscle, a localized induration of muscle, dermatographia and a reduction of pain with ethylchoride spray.[14] In electromyographic studies of 29 patients they found no evidence to indicate that muscle spasm was a cause of the localized muscle induration.

Thus there has been continuing point and counterpoint in the saga of fibrositis. It would seem that a major impetus to further study has been the consistent finding of the enigmatic "fibrositic nodule." Even here the occasional dissenting voice is heard; Heneh remarked that they were "only accessible to the finger of faith."[15] However, most workers have not denied the existence of these tender spots and indeed the first description goes back to 1843 and is accredited to the German physician Froriep.[16] In fact there is an extensive German language literature, attesting to the reality of these tender spots, which has recently been reviewed by Simons.[17] Given this historical background it is hardly surprising that the whole area of muscular rheumatism and fibrositis is often treated with some skepticism.

Diagnostic Evaluation

Patients with fibrositis complain of musculoskeletal pain and soreness of a predominantly proximal distribution. The pain can seldom be accurately localized and there is no history of joint swelling. It is inconsistent in location with a tendency to shift in position and vary in intensity. Muscle weakness is often claimed, but on closer questioning this is invariably a secondary response to pain and true weakness is not a problem. Morning stiffness and easy fatigability are usually prominent symptoms and mimic those seen in association with the classical inflammatory rheumatic disorders. Such patients are naturally concerned that they may be afflicted with a potentially crippling and incurable arthritic disease.

There are certain clues in the history which should suggest a possible diagnosis of fibrositis; these revolve around those factors that exert an exacerbating or ameliorating influence. Most of the patients will volunteer that their symptoms are aggravated by one or more of the following:

emotional stress, chronic fatigue, unaccustomed exertion, noise, bright lights, exposure to dampness or chilling, and unresolved conflicts or decisions. Improvement can occur with a hot bath or shower, massage, local application of heat, a holiday, gentle exercise and other diversionary activities. The history should always include information about potential initiating factors either real or imagined. It is not uncommon for the onset of fibrositis to be associated with an automobile or work-related accident. The perpetuation of symptoms by chronic anxiety, often in association with considerations of secondary gain, is difficult to evaluate and poses sensitive medicolegal issues.

It is important to gain some understanding of the effect of this disease on the patient's ability to work, perform the usual chores of daily living and pursue preferred recreational activities. An ability to make light of the symptoms and the continuation of a normal living pattern augur well for a good prognosis. Conversely a history of many days lost from work and a major disruption of the previous life-style usually indicate that effective treatment will be difficult.

Patients with fibrositis are often depressed, and specific questions and observations should be directed toward the following points: decreased energy, miserable or troubled facies, ponderous thinking, indecisiveness, loss of sexual interest, reduced appetite, constipation, feelings of inadequacy, suicidal ideas and inadequate sleep. Indeed, a nonrestorative sleep pattern may be a major contributing factor to the symptomatology of fibrositis (see section on pathophysiology).

The physical examination of a patient with fibrositis is notable for the lack of abnormal findings in contradistinction to the patient's history of pain and misery. Such patients usually relax poorly and complain of pain during the examination, but no specific changes are found in the joints and there is a well-preserved musculature. Such unrewarding examination findings in the context of the history should always suggest a diagnosis of fibrositis and direct attention to areas not routinely examined. Such areas are the so-called trigger points or tender spots. They are at locations over muscles and ligamentous bony insertions that are often tender but not painful in healthy persons. These areas should be firmly palpated by the examiner's thumb in a systematic manner while observing the patient's reaction. Symptomatic tender spots will usually elicit verbal expression of pain or a withdrawal response. There is often a reproduction of the patient's symptoms in a referred distribution. Smythe has described 14 typical sites of deep tenderness.[1,2] Other areas have often been noted and some 25 tender spots are shown in Figure 1.

One further finding should be sought, namely skin-fold tenderness over the upper scapular region. Rolling the skin between the thumb and index finger in this area is excruciatingly painful

TABLE 2.—*Diagnostic Guidelines*

History

Ill-defined musculoskeletal pain, often shifting in location.

Exacerbation of symptoms by stress, noise, cold, unaccustomed exercise and chronic fatigue.

Temporary relief of symptoms by heat and massage.

Prominent morning stiffness.

Chronic fatigue and poor work tolerance.

Nonrestorative sleep.

Initiation of symptoms by emotional or physical trauma.

Examination

Normal findings on joint examination.

Normal muscle mass and strength.

Tenderness over the "tender points." (See Figure 1.)

Skin-roll tenderness over upper scapular region.

Depressed affect.

Temporary relief of referred pain by infiltration of the trigger point with local anesthetic.

Normal ESR, SGOT, muscle enzymes, rheumatoid factor, ANF and appropriate findings on skeletal x-ray studies.*

ANF = antinuclear factor
ESR = erthrocyte sedimentation rate
SGOT = serum aspartate aminotransferase (serum glutamic oxaloacetic transaminase)

*When fibrositis is secondary, there will, of course, be abnormalities shown on x-ray studies.

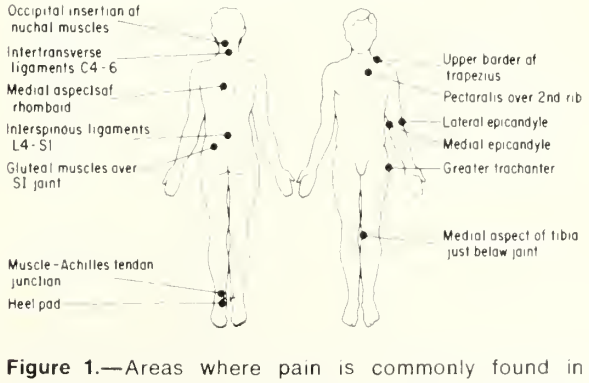


Figure 1.—Areas where pain is commonly found in patients with fibrositis. Palpations should be firm and the specificity of tenderness confirmed by palpation of an adjacent area. There are 25 representative points shown, making up 12 paired areas and one central area.

in patients with fibrositis and is often followed by a pronounced reactive hyperemia of the overlying skin.

Positive observations in the aforementioned areas should be controlled by equally firm palpation of adjacent areas.

Smythe has proposed a rigorous definition of fibrositis which would appear useful in controlled clinical studies[1]: (1) widespread aching for longer than three months; (2) local tenderness at 12 of the 14 specified sites; (3) skin-roll tenderness over the upper scapular region; (4) disturbed sleep with morning fatigue and stiffness, and (5) no abnormalities of erythrocyte sedimentation rate, serum aspartate aminotranferase (SGOT), rheumatoid factor, antinuclear factor and muscle enzymes, or on sacroiliac films.

These criteria are too strict for many patients who undoubtedly have fibrositis, and it is suggested that they be modified for general clinical use by altering item 2 to "local tenderness at 10 of the 25 specified sites" (see Figure 1). Furthermore, other investigations, in addition to those given in item 5, are sometimes indicated (see the section on differential diagnosis, which follows). One useful additional diagnostic maneuver is the local infiltration of a major tender spot with local anesthetic. This results in a temporary alleviation of the pain in the referred area and also serves as a convincing demonstration in explaining the nature of the disease to the patient. These diagnostic considerations are summarized in Table 2.

Differential Diagnosis

Psychogenic Rheumatism

The occurrence of persistent and often disabling symptoms, in the face of an ostensibly normal physical examination and normal laboratory studies, usually suggests major psychogenic factors. In this respect the seeking of painful tender spots and skin-fold tenderness is of paramount significance in differentiating fibrositis from true psychogenic rheumatism. This latter term is in itself imprecise as it encompasses a variety of nonorganic pain syndromes. Classical hysteria occurs in an attention-seeking, emotionally unstable egocentric personality, usually in response to some distressing experience, and offers little problem in diagnosis. Willful malingering is rare and can only be diagnosed with confidence in some self-mutilating patients or picturesque pathological liars, such as seen in the Münchausen syndrome. Nonwillful malingering is probably a very common occurrence in association with many musculoskeletal disorders and attests to the remarkable powers of human self-deception which persuade a patient of the validity of his own symptoms. Such patients invariably stand to gain some secondary benefit from the continued *illness:* by avoiding the tensions of ordinary life, by getting more love and attention than previously, by getting a pension or an insurance settlement. This is by no means uncommon in bona fide fibrositis patients and seems to be particularly common in middle-aged manual laborers with fibrositis; such patients cannot tolerate the idea of continuing hard work into their latter years and see a disability settlement as their only escape.

A final consideration concerning psychogenic rheumatism versus fibrositis is the concept of the unconscious symbolic use of pain. Such pain tends to be localized to a single region, which usually has emotional rather than segmental boundaries, such as the back, the neck, the hand, the heart or the chest. Descriptions of the pain are usually narrated in colorful and metaphorical language, often accompanied by dramatizing facial expressions and hand movements. A paradoxical association of numbness and tenderness is not uncommon. Such patients may have an underlying mental disease such as schizophrenia, psychopathic personality, organic psychosis, depression or various psychoneuroses. The diagnosis of "symbolic pain" does not rule out an underlying organic disease, but makes its diagnosis and management exceedingly difficult.

Secondary Fibrositis

Fibrositis not infrequently exists in conjunction with another disease or is secondary to some other condition. Some physicians consider that fibrositis is always a secondary phenomenon and that a diagnosis of primary fibrositis merely implies a lack of recognition of the underlying cause.

Generally speaking diseases that seem to predispose to fibrositis are those conditions which in themselves have fatigue as a prominent manifestation, such as rheumatoid arthritis, systemic lupus erythematosus, polymyalgia rheumatica, viral hepatitis, influenza, hypothyroidism and the like. It is certainly important to recognize these predisposing causes as some are self-limiting (such as viral hepatitis) while in others (such as sys-

temic lupus erythematosus) the profound fatigue may be ameliorated by low doses of prednisone (7.5 to 10 mg per day) with concomitant improvement in the fibrositis. It is the anecdotal experience of many rheumatologists that primary fibrositis is not benefited by prednisone administration; indeed a beneficial response should lead to reassessment of the diagnosis.

On the other hand fibrositis may complicate a well-developed rheumatic illness such as ankylosing spondylitis, rheumatoid arthritis, systemic lupus erythematosus or primary Sjögren syndrome. It is most important to recognize this occurrence because increased therapeutic efforts to control the primary disease are seldom effective in treating the fibrositis and may lead to unnecessary and undesirable side effects.

Similar But Distinct Pain Syndromes

The occurrence of pain over the medial and lateral condyles, exacerbated by gripping, is a common occurrence, as an isolated problem, and is referred to colloquially as golfer's elbow and tennis elbow respectively. Patients with fibrositis are seldom aware of tenderness in these situations until they are palpated; this is in contradistinction to patients afflicted with tennis or golfer's elbow.

Pain over the heel and Achilles tendon is a cardinal feature of Reiter disease and related seronegative spondyloarthropathies. However, such pain is virtually never seen in the absence of an oligoarticular arthritis or significant sacroiliitis. In such conditions the Achilles tendon is usually thickened, whereas it is of normal size and contour in fibrositis. Pain in these areas also occurs in joggers and may develop in other sites such as the patellotibial junction and over the greater trochanter. Ossification occurs at bone-tendon junctions in elderly patients with a distinctive band of ossification running down the right side of several contiguous thoracic vertebrae. This was originally referred to as Forestier disease[18] and is now more commonly referred to as diffuse idiopathic skeletal hyperostosis (DISH).[19] These patients often have pain at the back of the occiput, the greater trochanter, ischia, ilia and calcanei.

Patients who have been receiving corticosteroids for long periods often complain of vague arthralgias and myalgias on attempted dose reduction. This has been referred to as "steroid pseudorheumatism."[20] Furthermore they often complain of a pronounced tenderness of the muscles of the extremities and have extreme sensitivity to pressure over the shins.

TABLE 3.—*Partial Differential Diagnosis of Fibrositis*

Secondary to Rheumatic Diseases
Rheumatoid arthritis
Ankylosing spondylitis
Systemic lupus erythematosus
Polymyalgia rheumatica
Primary Sjögren syndrome
Polymyositis
Osteoarthritis of the spine
Secondary to Fatiguing Illnesses
Influenza
Viral hepatitis
Infectious mononucleosis
Subacute bacterial endocarditis
Brucellosis
Inflammatory bowel disease
Endogenous depression
Mimicking Diseases
Seronegative spondyloarthropathies
Athletic overuse syndromes
Forestier disease-DISH
The enthesopathies (tennis elbow, etc.)
Hypothyroidism
Osteopenia/osteomalacia
Psychogenic syndromes
Steroid pseudorheumatism
Narcotic withdrawal syndrome
Polymyalgia rheumatica

DISH = diffuse idiopathic skeletal hyperostosis

Elderly postmenopausal women with a combination of osteoporosis and osteomalacia not infrequently complain of total body pain and there is tenderness to pressure over both bone and muscle. They do not usually have the characteristic tender spots of fibrositis, although this can occur as a secondary phenomenon.

Hypothyroidism with myxedematous infiltration of muscle occasionally presents with muscular aching and soreness.[21] The histological finding of interfascicular mucopolysaccharides is strikingly similar to that found in fibrositic nodules (see section on pathophysiology). These differential diagnostic considerations are summarized in Table 3.

Some Pathophysiologic Considerations

At present there are no generally accepted pathognomonic changes in muscle histology, electromyography, blood tests or psychophysiologic testing that can be claimed to characterize fibrositis. However, there have been some intriguing advances in the pathophysiology and biochemistry of pain, sleep disturbances and muscle histology,

which may be of some relevance to unraveling the enigma of fibrositis.

Sleep Disturbance and Central Nervous System Serotonin Metabolism

Moldofsky and colleagues[22] have made the interesting observation that patients with fibrositis have a reduced amount of non-rapid eye movement sleep (non-REM sleep). This seems a particularly pertinent observation as a complaint of nonrestorative sleep is commonplace in fibrositic patients. Furthermore, they have induced musculoskeletal pain, similar to fibrositis, in healthy volunteers by depriving them of non-REM sleep.[23] Of particular interest was the finding, in a pilot study, that in very fit persons (those running two to seven miles every day) fibrositic symptoms did not develop.

A recent study has shown that physically fit persons have a higher level of non-REM sleep than unfit subjects and that following exercise the amount of non-REM sleep increased in fit, but remained unchanged in unfit subjects.[24]

There is increasing evidence in animals and humans that serotonergic neurotransmission plays a central role in the regulation of non-REM sleep, pain sensitivity and affective states.[25] Moldofsky has proposed that a disturbance of central nervous system serotonin metabolism may underlie the non-REM sleep, the heightened pain perception and depressive symptoms in patients with fibrositis.[22] Indeed in a small study involving eight fibrositic patients he showed an inverse relationship between plasma-free tryptophan and subjective pain.[26]

Enkephalins, Substance P and the Gate Theory of Pain

It is becoming increasingly evident that there exists a set of powerful endogenous mechanisms of pain control.[27] The amelioration of pain by acupuncture, massage and transcutaneous nerve stimulation may well be due to activation of these endogenous antinociceptive mechanisms.[28] The endogenous morphine-like substances, the enkephalins and endorphins are generally considered to be the prime mediators of this phenomenon.[29] On the other hand it appears that *substance P* (initially discovered by Von Euler in 1931), a small peptide of 11 amino acid residues, may be the major neurotransmitter for pain signals.[30] It has been shown that substance P is present in the small diameter nerve fibers of the dorsal horn, which have traditionally been considered to be pain fibers. Particularly high concentrations of substance P are found in the substantia gelatinosa, that region of the dorsal horn that has been implicated in the *gate theory* of pain modulation.[31] The synthetic enkephalin analogue (Met-enkephalin) blocks the release of substance P and this effect is blocked by naloxone. Descending neurons utilize serotonin as a neurotransmitter and are thought to modulate pain perception through the gate control mechanism at the level of the substantia gelatinosa.[32]

It is now firmly established that stimulation of the brain activates descending efferent fibers which in turn influence afferent conduction of pain and other sensations.[33] In this way it is possible for cerebral functions subserving emotion, attention and memories of past experience to exert control over sensory input. For example, men wounded in battle may feel no pain from their wound, because favorable descending impulses block pain perception—they survived the battle and for this they are grateful. On the other hand they may complain vociferously about an inept venipuncture.[34]

In what manner these newer ideas on pain may be applicable to fibrositis can only be speculative at this time. The traditional emphasis on pain fiber stimulation via tissue disease, with a relative neglect of the motivational and cognitive contributions, has probably sidetracked us from the core of the issue.

The Fibrositic Nodule

Although Hench considered fibrositic nodules "only accessible to the finger of faith,"[15] it is generally accepted that band-like or nodular thickenings are a commonly encountered finding in fibrositis.[17] Their presence poses two, as yet unanswered, questions: what is their nature and what role, if any, do they play in the pathogenesis of symptoms?

It has been the experience of most investigators that muscle biopsy of fibrositic patients is unrewarding in terms of conventional staining techniques and that the inflammatory changes found by Stockman[4] are not present. However, there are two independent reports on biopsies of actual fibrositic nodules that indicate that the palpable induration may be due to local edema and the interfascicular deposition of acid mucopolysaccharides.[35,36] Electromyography, with monopolar needle insertion directly into the fibrositic nodule,

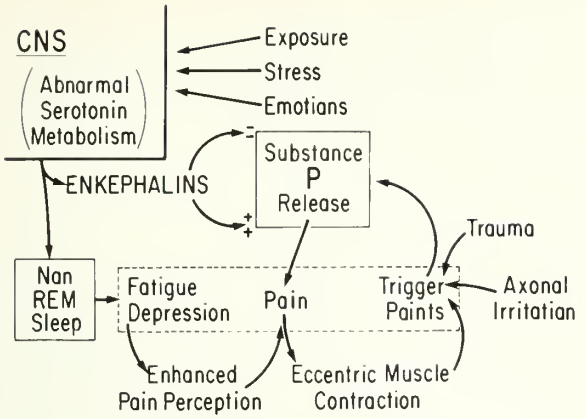


Figure 2.—A schematic representation of some of the factors that are possibly relevant to the psychopathophysiology of fibrositis. The features within the dotted rectangle are the common clinical findings in fibrositis. CNS = central nervous system. REM = rapid eye movement (sleep).

showed polyphasic motor unit action potentials in six of ten cases.[36] The fact that fibrositic nodules are still palpable in curarised patients and persist after death, until obscured by rigor mortis[37] is strong evidence against their being primarily local muscle spasm. The inconsistent muscle hyperreactivity, found on electromyography, may well be a fluctuating response to a painful trigger point and account for the shifting nature of fibrositic pain and its amelioration by activities which promote muscular relaxation.

Deep Hyperalgesia

The pain experienced in fibrositis is referred pain of deep origin and does not correspond to a dermatomal distribution. Such pain is poorly localized and is often associated with feelings of heaviness, a tingling sensation or a swollen feeling. Most deep pain is referred distally often at some distance from the site of origin; the distribution patterns of such pain are well described in Kellgren's pioneering studies of this subject.[38]

It is generally assumed that the fibrositic nodule or the tender spot at bone-tendon insertion is a trigger point for the referred pain in fibrositis. The fact that local anesthetic infiltration of such an area usually affords some temporary relief of pain supports this hypothesis. The existence of the fibrositic nodule is often used as evidence for fibrositis being an organic disease of muscle. However, it seems more likely that it is an inconsistent phenomenon secondary to the previously described neuropsychiatric changes, but when present may well play a role in perpetuating the pain syndrome. Figure 2 is an attempt to bring together some of these facts into one central hypothesis.

Treatment

Fibrositis is an extraordinarily difficult condition to treat effectively, indeed most physicians are more successful at treating a complicated case of systemic lupus erythematosus than fibrositis. This most surely stems from an undue reliance on medications and inadequate time given to explanation to patients. Patients with fibrositis are naturally concerned that their musculoskeletal pain is the harbinger of a serious illness or crippling arthritis. They feel threatened by their prospects for the future, the effect of fatigue upon their work and recreational activities, and the lack of effectiveness of the prescribed medications. This latter point is especially important in those who have long-standing fibrositis; they invariably resort to doctor shopping and paramedical treatment. Not unnaturally, they become disenchanted and skeptical of the medical profession.

First and foremost in treatment is a thorough history and physical examination along with some carefully chosen investigations (albeit elaborate investigational studies are seldom indicated). This is a prerequisite to gaining the patient's confidence as well as gaining important insight into provocative factors and an understanding of what effect the disease is having on the patient's life. A careful explanation of the nature of fibrositis is then called for, emphasizing the following points: (1) lack of crippling or serious illness, (2) the concept of referred pain and trigger points (can often be dramatically conveyed by local anesthetic injection), (3) the nonrestorative sleep disturbance and its relationship to fatigue, (4) the role of aggravating and ameliorating factors on the fluctuation of symptoms and (5) a heightened self-awareness of the patient's own attitudes and expectations. The intellectual level of the discussion must be carefully adjusted to the patient's own level of intelligence. In particular it is most important to avoid the impression that the symptoms are primarily of emotional origin; this will be taken by most patients to imply that they are imagining their pain or malingering. With time and an increased understanding of the disease process, most patients come to appreciate the importance of the underlying emotional currents in their own case. This realization should come about gently and naturally without overt prodding

by the physician. However, where there are obvious gains to be derived from the illness or the patient is a nonwillful malingerer, an early but sympathetic exposure is mandatory, if further progress is to be made.

Most patients will already have tried aspirin or similar medications; in most cases they are of minimal help, and there is little use in prescribing a long line of nonsteroidal anti-inflammatory agents; in fact, there is every reason not to, in terms of professional credibility. Many patients will be helped by a tricyclic antidepressant at night. This appears to improve the restorative quality of sleep and patients report feeling less fatigued and more able to cope with their pain. They are often less tolerant of such medications than most patients and it is best to start at a relatively low dose (for example, 10 to 25 mg of amitriptyline). Tranquilizers seem to be of little benefit in most cases and there seems to be an aversion for such medications in the personality make up of many fibrositic patients. Cyclobenzaprine, a centrally acting muscle relaxant, is sometimes of some benefit; it is given in a dosage of 10 mg in the early evening and before retiring—drowsiness usually precludes its use during the day. Injection of trigger points with a local anesthetic, with or without hydrocortisone, is only a temporizing measure and its frequent usage fosters undue dependency on the physician. Repeated injections in the same area may well produce a focus of irritation, but this is not proved.

Some patients are benefited by relaxation classes, but in the absence of a good understanding of their disease, this form of therapy is only of temporary benefit; the same can be said for physical therapy, heat applications, massage and acupuncture.

Many of the problems encountered in treating fibrositis seem to originate from the adoption of the expected stereotyped roles of patient and doctor. Talcott Parsons, a Harvard sociologist, has defined the sick role under four headings: (1) the sick person is exempted from some or all of his normal activities and duties, (2) the sick person cannot help being ill and cannot get well by willpower alone, (3) the sick person is expected to want to get well as soon as possible and (4) the sick person is expected to seek appropriate help and cooperate in an effort to get well.[39]

The patient with fibrositis seems to act out this sick role par excellence; the physician's role is best served by placing the burden of improvement on the patient and not on drugs. It is a delicate and precarious dance of readjusting both psyche and soma; a true test of both the art and science of medicine.

Conclusions

The fibrositic misnomer has been a disservice to the widespread recognition and research of an ubiquitous affliction. Moldofsky has proposed the term "nonrestorative sleep syndrome," in recognition of one important aspect of its psychopathophysiology. Smythe regards it as a disorder of pain modulation and uses the term "pain amplification syndrome."[40] These terms are preferable to fibrositis but do not explain such somatic elements as the "fibrositic nodule." For the time being a noncommittal term as regards pathogenesis, such as the old term *muscular rheumatism,* would be preferable. It is to be hoped that the burgeoning increase of knowledge of the psychopathophysiology of pain will lead to a better understanding of the fibrositis syndrome. Whatever we call it, it will not go away just because we may choose to ignore it.[41]

REFERENCES

1. Smythe HA: Non-articular rheumatism and psychogenic musculoskeletal syndromes, *In* McCarty DJ (Ed): Arthritis and Allied Conditions, 9th Ed. Philadelphia, Lea & Febiger, 1979, pp 881-891

2. Smythe HA, Moldofsky H: Two contributions to understanding the "fibrositis syndrome." Bull Rheum Dis 28:928-931, 1978

3. Gowers WR: Lumbago: Its lessons and analogues. Br Med J 1:117-121, 1904

4. Stockman R: The causes, pathology and treatment of chronic rheumatism. Edinburgh Med J 15:107-116, 223-235, 1904

5. Abel O Jr, Siebert AJ, Earp R: Fibrositis. J Missouri Med Ass 36:435-437, 1939

6. Collins DH: Fibrositis and infection. Am Rheum Dis 2: 114-126, 1940

7. Slocumb CH: Fibrositis. Clinics 2:169-178, 1943

8. Llewellyn LJ, Jones AB: Fibrositis. London, Heinemann, 1915

9. Stockman R: Rheumatism and Arthritis. Edinburgh, W Green, 1920

10. Elliott FA: Tender muscles in sciatica: Electromyographic studies. Lancet 2:47-49, 1944

11. Kelly M: The nature of fibrositis. Am Rheum Dis 5:69-77, 1946

12. Copeman WSC, Ackerman WL: Fibrositis of the back. Q J Med 13:37-51, 1944

13. Copeman WSC, Ackerman WL: Edema or herniations of fat lobules as a cause of lumbar and gluteal "fibrositis." Arch Intern Med 79:22-35, 1947

14. Kraft GH, Johnson EW, LaBan MM: The fibrositis syndrome. Arch Phys Med 49:155-162, 1968

15. Hench PS, Bauer W, Fletcher AA, et al: Fibrositis in "Review of the American Literature for 1935." Ann Intern Med 10: 878-884, 1936

16. Froriep H: Ein Beitrag zur Pathologie und Therapie des Rheumatismus. Weimar, 1843

17. Simons DG: Muscle pain syndromes, Part 1. Am J Phys Med 54:289-311, 1975

18. Forestier J, Rotes-Querol J: Senile ankylosing hyperostosis of the spine. Ann Rheum Dis 9:321, 1950

19. Resnick D, Niwayama C: Radiographic and pathological features of spinal involvement in diffuse idiopathic skeletal hyperostosis (DISH). Radiology 119:559-568, 1976

20. Rotstein J, Good BA: Steroid pseudorheumatism. Arch Intern Med 99:545-555, 1957

21. Golding DN: Hypothyroidism presenting with musculoskeletal symptoms. Ann Rheum Dis 27:10-14, 1970

22. Moldofsky H, Scarisbrick P, England BA, et al: Musculoskeletal symptoms and non-REM sleep disturbance in patients with "fibrositis syndrome" and healthy subjects. Psychosomatic Med 37:341-351, 1975

23. Moldofsky H, Scarisbrick P: Induction of neurasthenic musculoskeletal pain syndrome by selective sleep stage deprivation. Psychosomatic Med 38:35-44, 1976

24. Griffin SJ, Trinder J: Physical fitness, exercise and human sleep. Psychophysiology 15:447-450, 1978

25. Chase TN, Murphy DI: Serotonin and central nervous system function. Ann Rev Pharmacol 13:181-197, 1973

26. Moldofsky H, Warsh JJ: Plasma tryptophan and musculoskeletal pain in nonarticular rheumatism ("fibrositis syndrome"). Pain 5:65-71, 1978

27. Liebeskind JC, Paul LA: Psychological and physiological mechanisms of pain. Ann Rev Psychol 28:41-60, 1977

28. Mayer D, Price DD, Rafii A: Antagonism of acupuncture analgesia in man by the narcotic antagonist naloxone. Brain Dis 121:368-372, 1977

29. Terenius L: Endogenous peptides and analgesia. Ann Rev Pharmacol 18:189-205, 1978

30. Marx JL: Brain peptides: Is substance "P" a transmitter of pain signals? Science 205:886-889, 1979

31. Melzack R, Wall PD: Pain mechanisms: A new theory. Science 150:971-979, 1965

32. Besson JM, Guilbond G, Le Bars D: Descending inhibitory influences exterted by the brainstem upon the activities of dorsal horn lamina—V. Cells induced by intra-arterial injection of bradykinin into the limbs. J Physiol 248:725-739, 1975

33. Del Bianco DL, Del Bene E, Sicuteri F: Heart pain, *In* Bonica JJ (Ed): Advances in Neurology, Vol 4. New York, Raven Press, 1974, pp 375-381

34. Abraham VC: An induction of prolonged change in the functional state of the spinal cord, *In* Bonica JJ (Ed): Advances in Neurology, Vol 4. New York, Raven Press, 1974, p 243

35. Brendstrup P, Jespersen K, Asboe-Hansen G: Morphological and chemical connective tissue changes in fibrositic muscles. Ann Rheum Dis 16:438-440, 1957

36. Awad E: Interstitial myofibrositis: Hypothesis of the mechanism. Arch Phys Med Rehabil, 54:449-453, 1973

37. Schade H: Beitrage zur Umgrenzung and Klarung einer Lehre von der Erkaltung. Z Ges Ech Med 7:275-374, 1919, cited in Simons DG[17]

38. Kellgren JA: Observation on referred pain arising from muscle. Clin Sci 3:175-190, 1938

39. Parsons T: The Social System. New York, Free Press, 1964

40. Smythe HA: "Fibrositis" as a disorder of pain modulation, *In* Dixon AS (Ed): Clinics in Rheumatic Diseases, Vol 5. Philadelphia, WB Saunders Company, 1979, pp 823-832

41. Rosenbaum EE: Rheumatology. New York, Medical Examination Publishing Co Inc, 1980, p 219

Mammography and Breast Disease

I THINK MAMMOGRAPHY is a very important advance in the management of patients with breast disease. The pendulum swings back and forth, of course. I consider it an important adjunct to the physical examination. It is an examination like anything else and must be looked upon as that. In any patient who has a lump, a mass that the examiner feels is discrete, a biopsy must be done regardless of what mammography shows. And in fact, I do not do mammography in patients who have a mass—I do a biopsy. Mammography is to look for nonpalpable disease. When a patient has a mass that turns out to be carcinoma on biopsy, I then do a mammogram primarily to look at the other breast and to look at this breast to see if there is any other lesion and for subsequent follow-up of the other breast, which I then do once a year for any treatment of primary breast cancer. Patients with disease that is not clearly discernible as a mass, but you are concerned about what you're feeling in the breast, that is where mammography can be very helpful. It is helpful because it can find things that you cannot feel or help push you to carry out a biopsy when you cannot feel anything wrong. I think the biggest problem in mammography is that in young women it is not very useful, because the density of the breast is such that it does not allow itself to show other disease through the dense normal breast tissue. Under the age of 35, I do not believe very many people should have mammographies, just women in whom breast cancer has been diagnosed. High-risk factors, other malignant conditions that might predispose a patient to breast cancer development and certain other factors may justify doing mammography in patients younger than 35, but very few people need it. From 35 to 50, I think women with genetic risk factors should probably have a mammogram once a year or at least every two years. And over the age 50, I think any woman that has any breast abnormality should have a mammogram. . . . Now, if the mammogram shows abnormalities which the mammographer is concerned about, in the form of stippled calcification and the formation of a mass lesion which you cannot feel, you are obligated to do a biopsy. Likewise, failure to take a biopsy specimen of a lesion when the mammogram does not show anything is also a very dangerous procedure. So I think mammograms and physical examinations complement each other. They will both identify disease and they should both be used appropriately.

—RICHARD E. WILSON, MD, *Boston*

Extracted from *Audio-Digest Surgery*, Vol. 27, No. 13, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1577 East Chevy Chase Drive, Glendale, CA 91206.

Specialty Conference

Refer to: Lindsay KL, Reynolds TB, Hoefs JC, et al: Ascites—University of Southern California and Rancho Los Amigos Hospital, Downey, California (Specialty Conference). West J Med 134:414-423, May 1981

Participants

KAREN L. LINDSAY, MD
TELFER B. REYNOLDS, MD
JOHN C. HOEFS, MD
MIGUEL E. SANMARCO, MD

From the Divisions of Hepatology and Cardiology, University of Southern California School of Medicine and the Rancho Los Amigos Hospital, Downey, California.

Ascites

WHEN *this specialty conference was given at the Los Angeles County-University of Southern California* (LAC-USC) *Medical Center Internal Medicine Grand Rounds, the case was presented in three parts using a protocol with stapled pages allowing members of the audience to work through the case in a manner simulating the actual patient's care. Although we are unable to reproduce such a format here, we encourage the reader to pause at the end of each section and formulate his or her own thoughts before proceeding to the next part.*

KAREN L. LINDSAY, MD:* A 56-year-old Mexican-American woman was referred to the LAC-USC Liver Unit on February 4, 1980, for evaluation of ascites.

She had been well until approximately February 1979, when pronounced abdominal swelling developed, which has remained since then. This condition was treated with diuretics, salt restriction and several paracenteses, but each time the fluid was removed, the swelling recurred. There was no pain, only a feeling of distention, some fatigue and mild shortness of breath on exertion while her abdomen was very swollen. Her appetite had remained good. She did not think she had lost any flesh but had not kept track of her weight.

She had never had jaundice, blood transfusions or hepatitis and drank alcoholic beverages rarely.

She had been admitted to a nearby hospital several times for paracentesis. Diagnoses made while she was there included the following: ascites of uncertain cause, mild hypertension, organic heart disease, adult-onset diabetes mellitus and mild renal insufficiency. At that time she was taking the following medications: 0.25 mg of digoxin each day, 50 mg of spironolactone twice a day and 80 mg of furosemide twice a day.

A review of bodily systems gave negative results except for the complaints mentioned above. She stated that she had no urinary symptoms, orthopnea, nocturnal dyspnea, chest pain or edema of the ankles. She had undergone a cesarean section in 1957, an appendectomy in 1964, a cholecystectomy in 1970 and an umbilical hernia repair in 1978.

On examination the patient was obese, with a blood pressure of 124/76 mm of mercury, heart rate of 72 beats per minute, temperature 36.7°C (98°F), respirations 20 per minute, height 144.8 cm (4 ft, 11 in), weight 87.5 kg (192.5 lb). Examination of the skin showed no spider angiomata or palmar erythema. The thyroid gland was not palpable. Neck veins were distended 4 cm above the clavicle at 45° of (head) elevation. She was able to lie flat without shortness of breath, however. On examination of the heart, the point of maximal impulse was not palpable, heart tones were distant but normal and a grade 2/6 systolic ejection murmur was heard at the lower left sternal border. The abdomen was substantially distended with shifting dullness. Old midline and right upper quadrant subcostal scars were present. There were no dilated veins, bruits or masses, and the liver and spleen were not palpable or

No reprints available.
*Clinical Research Fellow in Hepatology.

ABBREVIATIONS USED IN TEXT

Asc:S = ascites to serum ratio
CEA = carcinoembryonic antigen
LDH = Lactic dehydrogenase
$(S\text{-}Asc)_A$ = serum-to-ascites albumin concentration gradient
$(S\text{-}Asc)_{OP}$ = serum-to-ascites oncotic pressure gradient

ballotable. Trace pedal edema was present bilaterally. The remainder of the examination gave normal results.

The hemoglobin was 9.8 grams per dl, leukocyte count 6,200 per cu mm and platelet count normal. The serum albumin was 3.7 and globulin 3.6 grams per dl; alkaline phosphatase 1.6 Bessie Lowry units (normal 1 to 3); total bilirubin 2.0 and direct bilirubin 1.2 mg per dl; aspartate aminotransferase (SGOT) 7 and alanine aminotransferase (SGPT) 7 Sigma Frankel units; lactic dehydrogenase (LDH) 113 units per liter; urea nitrogen 57, creatinine 1.5, uric acid 12.4 and glucose 148 mg per dl. Prothrombin was 67 percent. Serum levels of sodium, potassium, chloride, carbon dioxide, calcium and phosphate were normal.

At this point the reader may wish to pause for a few minutes to consider the possible causes of ascites in this patient and how to proceed in further evaluation. Then Dr. Reynolds will discuss the differential diagnosis of ascites and his approach to the evaluation of a patient with ascites.

TELFER B. REYNOLDS, MD:* The most prominent finding in our patient was ascites, a gross abnormality with a limited number of causes; thus, the cause should always be determined. In this patient there is no doubt about the presence of ascites (Figure 1). With less distention or with an obese abdomen there may be difficulty in deciding whether or not this condition is present. Helpful clues are shifting flank dullness and the patient's recognition that there has been weight gain associated with increased abdominal girth. A large ovarian cyst can simulate ascites but there will be tympany in the flanks due to displaced bowel and dullness centrally. Search for a "fluid wave" is of little value because this physical finding is only present when ascites is tense and obvious. Examination of sodium balance is very useful in assessment of ascites. When ascites is forming, the concentration of sodium in urine is invariably low. There will be a rapid weight gain with ingestion or intravenous administration of sodium, and there may be rapid weight loss with a combination of sodium restriction and diuretic therapy. Diagnostic paracentesis is relatively safe and easy and can be used to prove the presence of ascites as well as to aid in determining its cause. For this procedure, I prefer the left lower quadrant or the midline below the umbilicus for insertion of a 21-gauge needle. One should attempt to avoid injury to the liver, an enlarged spleen, epigastric arteries and veins, visible collateral veins and invisible collateral veins that may be present in adhesions under abdominal scars. Ultrasound testing and computed tomography are noninvasive techniques that are reliable in demonstrating ascites, but it should rarely be necessary to use such expensive tests to settle a relatively simple point.

Although there are many different causes for

Figure 1.—Side view of patient showing massive ascites and distention of the abdomen.

*Loosli Professor of Medicine.

ascites, our diagnostic acumen may be dulled by the fact that chronic liver disease is by far the most common of these. Therefore, unless we consider *all* the possible causes (Table 1) and routinely carry out diagnostic paracentesis each time we encounter ascites, we are likely to overlook the unusual causes. Some of these are quite treatable.

Peritoneal carcinomatosis as a cause of ascites may be suspected from the clinical history but, more often, is suggested by the findings of diagnostic paracentesis. Protein content is invariably high, the level of lactate dehydrogenase usually is high and the carcinoembryonic antigen (CEA) level may be very high. The fluid may be viscous and feel "slimy." Omental masses are often palpable when the abdominal distention is relieved. Carcinoma can produce ascites by a different mechanism—diffuse embolization of the portal circulation that results in portal hypertension. In such cases the ascitic fluid will resemble that formed in chronic liver disease. This type of ascites may defy diagnosis until evidence of malignancy is found in some other manner.

Cardiac ascites usually is due to constrictive pericarditis or to tricuspid incompetence. Constrictive pericarditis may be particularly difficult to diagnose because ankle edema or significant exertional dyspnea is often absent. The neck veins are the key to diagnosis. Invariably, they are distended in constrictive pericarditis and grossly pulsatile in tricuspid incompetence, if the patient is examined in the sitting position. The protein content of cardiac ascites tends to be high as Dr. Hoefs will explain later.

Pancreatic ascites is caused by leakage from a pancreatic pseudocyst. The only feature that is diagnostic is a high amylase content in the fluid.

Tuberculous ascites is important to recognize because of its treatability. We still see two or three cases annually at LAC-USC Medical Center. Most patients have fever and a high protein content in the ascitic fluid. Culture of the ascitic fluid is sometimes rewarding if a large enough volume is sent for laboratory study. Even more valuable is biopsy and culture of a peritoneal specimen, obtained either by the Cope-needle technique or at peritoneoscopy. Both of these procedures carry some risk because of the frequency of intestinal adhesion to the anterior abdominal wall when there is tuberculous inflammation. In some patients peritoneal tuberculosis is superimposed on chronic alcoholic liver disease; in this situation, the ascites may be caused primarily by portal hypertension in which case the protein content of the fluid may not be high. The diagnosis of tuberculosis is often missed in this type of patient unless a meticulous workup for unexplained fever is carried out.

On rare occasions, *coccidioidomycosis* may cause ascites with similar symptoms and findings as in patients with tuberculosis. The complement fixation test for coccidioidal organisms will be positive and results of peritoneal biopsy may disclose spherules in granulomas.

Occasionally, ascites results from *myxedema.* The clinical diagnosis can be missed only if it is not considered. The protein content of the fluid is invariably high. The relaxation phase of the deep tendon reflexes is grossly slowed.

Nephrogenous ascites is seen in an occasional patient with chronic uremia being treated with either hemodialysis or peritoneal dialysis. There is no satisfactory explanation that I am aware of for nephrogenous ascites and there is nothing diagnostic about the ascitic fluid. Though it is by far the most likely reason for the appearance of ascites in a patient with symptoms of chronic uremia, there may be reason to consider other diagnoses such as chronic hepatitis or tuberculous peritonitis.

Chylous ascites results from rupture of the cisterna chyli or the more distal lymphatic vessels draining the intestine and is usually due to trauma or a malignant lesion. This diagnosis will be made only if the fluid is examined. It will be milky in appearance and the triglyceride content will be several hundred mg per dl or higher.

Pseudochylous ascites is also lactescent but less white in color and contains no excess of triglyceride. Patients with pseudochylous ascites usually have chronic liver disease, and I am unaware of any explanation for the lactescence of the fluid. Differentiation between chylous and pseudochylous fluids often can be made at the bedside by adding petroleum ether to the fluid and shaking it vigorously. With chylous ascites, the triglyceride dissolves in the ether layer and the fluid becomes clear.

Eosinophilic gastroenteritis is a rare cause of ascites, when the process involves the peritoneum. A differential leukocyte count on the ascitic fluid invariably shows a high proportion of eosinophils if the cells are appropriately stained.

Portal vein occlusion sometimes results in ascites, most often after hemorrhage from esophageal

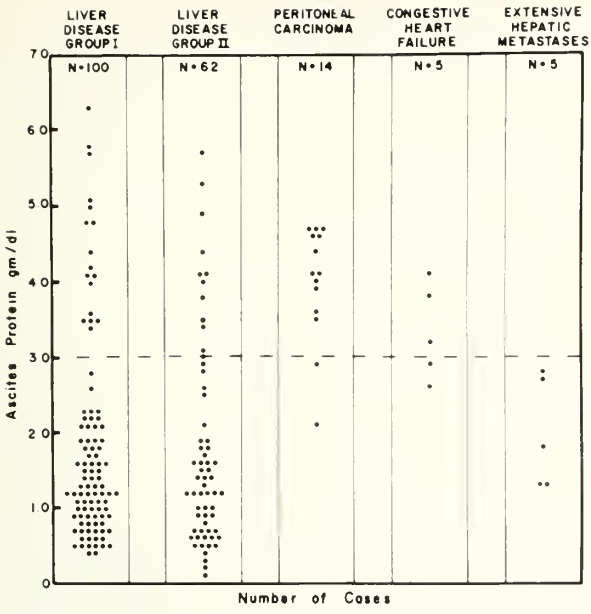


Figure 2.—Protein levels of ascitic fluid. (Reprinted with permission from Boyer T, et al: Archives of Internal Medicine 138:1104, July 1978; copyright 1978, American Medical Association.[2])

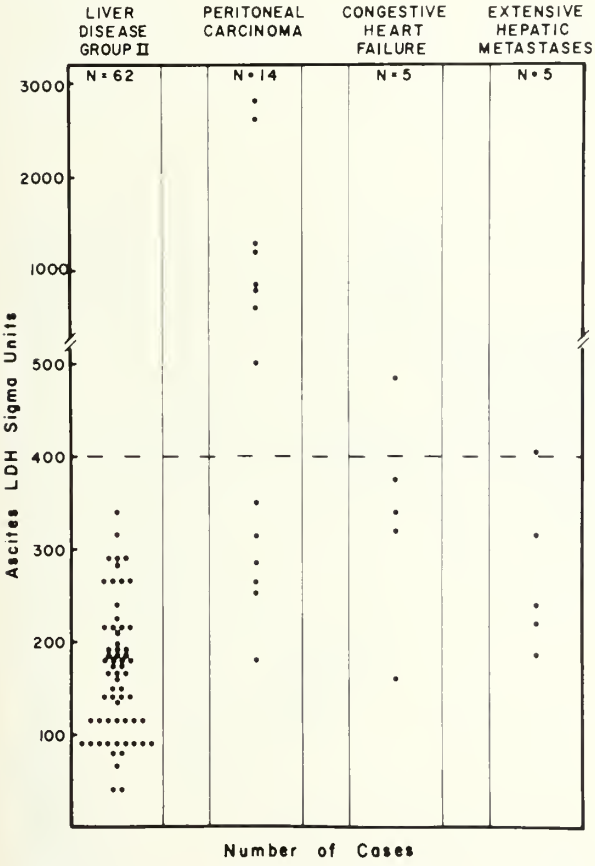


Figure 3.—Lactate dehydrogenase levels of ascitic fluid. (Reprinted with permission from Boyer T, et al: Archives of Internal Medicine 138:1104, July 1978; copyright 1978, American Medical Association.[2])

varices. In such a patient the presence of esophageal varices and the absence of any signs of liver disease may suggest the diagnosis, which can be confirmed with celiac or superior mesenteric angiography.

Hepatic vein thrombosis almost invariably results in ascites. There will be evidence of liver disease, but often a clinician will fail to consider hepatic vein occlusion unless there is right upper quadrant pain, liver biopsy results that indicate intense perivenular congestion or a liver-spleen scan that suggests caudate lobe hypertrophy. In our experience, ascitic fluid protein level is usually similar to that seen in ascites due to chronic liver disease.

Diagnostic paracentesis is the most important tool for determining the cause of ascites and it should be done in every patient in whom there is any doubt about the diagnosis. Light and colleagues[1] found three criteria useful in separating inflammatory from noninflammatory pleural effusions: (1) a pleural fluid-to-serum protein ratio greater than 0.5, (2) a pleural fluid LDH level greater than 200 IU and (3) a pleural fluid-to-serum LDH ratio greater than 0.6. Boyer and coworkers applied the same criteria to the differential diagnosis of ascitic fluid with fairly good results.[2] However, Figure 2, from Boyer's paper, shows the wide range in protein content in ascitic fluid of patients with uncomplicated liver disease and points to the difficulty of using protein content to confirm the diagnosis. Others have noted this same problem previously.[3,4] Later Dr. Hoefs will discuss the control of protein concentration in ascites fluid and will explain how to get maximum diagnostic information from the protein levels.

The LDH level is high in most malignant effusions and is rarely high in other conditions (Figure 3). Ascites leukocyte count is of little value in the differential diagnosis but of great value in pointing to the presence of spontaneous bacterial peritonitis. This is not a *cause* of ascites but, rather, a serious and frequently unsuspected complication of ascites with chronic liver disease. It has also been reported as a complication of ascites due to the nephrotic syndrome in children. A total number of polymorphonuclear cells greater than 250 per cu mm is suggestive enough of spontaneous bacterial peritonitis to justify antibiotic treatment pending the result of cultures. A high total leukocyte count with a low percentage of polymorphonuclear cells is moderately suggestive of tuberculous or carcinomatous ascites; however, the

normal range of leukocytes in ascitic fluid is rather broad in chronic liver disease. Also, as Dr. Hoefs has shown, the total leukocyte count rises with concentration of ascites fluid during diuresis.[5] The carcinoembryonic antigen (CEA) level in ascitic fluid is diagnostic of malignancy if very high (more than 100 ng per ml). The amylase level of ascitic fluid should always be measured because this may be the only clue to pancreatic ascites. Other diagnostic tests that can be ordered on ascitic fluid include cytology, culture for acid-fast bacilli and culture for bacteria. Because they are more expensive, they probably should be requested only when there is clinical suspicion of carcinoma or tuberculosis or when the ascites protein level is elevated.

To summarize the diagnostic approach to ascites—in a woman, always (1) percuss the flanks to look for ovarian cyst; (2) look at the neck veins to rule out cardiac ascites; (3) check the deep tendon reflexes to exclude myxedema, and (4) do a diagnostic paracentesis. After the fluid is obtained, always measure protein content, LD and amylase levels, leukocyte count and differential. Fluid should also be tested for CEA level, bacterial and acid-fast bacilli cultures and cytology if indicated by the clinical findings.

Our patient had ascites for more than a year. A malignant cause seems unlikely because of her relatively benign course. None of the clinical findings or laboratory test results are pathognomonic of chronic liver disease, but this remains a strong possibility. If she has chronic liver disease, it could be cryptogenic cirrhosis or cirrhosis due to hepatitis B. Despite the absence of right upper quadrant pain, she might have the Budd-Chiari syndrome due to hepatic venous occlusion. The duration of her illness is rather long for pancreatic ascites, but this is also a possibility. The presence of neck vein distention at 45° is intriguing and raises the possibility of constrictive pericarditis. Alternatively, she could have both heart and liver disease due to amyloid infiltration or hemochromatosis, or she could have coronary artery disease and cirrhosis coincidentally.

Further evaluation should begin with a diagnostic paracentesis. Serum HBsAg and thyroxine with thyroid-stimulating hormone (TSH) studies would be useful. The neck veins should be inspected closely for Kussmaul sign. A roentgenogram of the chest should be examined for pericardial calcification; cardiac fluoroscopy and echocardiography would also be helpful in assessing the pericardium. A liver-spleen scan would be helpful in deciding whether she has chronic liver disease.

DR. LINDSAY: Roentgenograms of the chest

Figure 4.—Posteroanterior (left) and lateral (right) roentgenograms of the chest showing cardiomegaly with 1+ prominence of the interstitial markings.

TABLE 1.—*Causes of Ascites*

Transudative	*Exudative*
Heart failure (tricuspid incompetence or constrictive pericarditis)	Peritoneal carcinomatosis
Inferior vena caval occlusion above hepatic veins	Tuberculous peritonitis
Hepatic vein occlusion	Coccidioidal peritonitis
Veno-occlusive disease of the liver	Pancreatic ascites
Chronic liver disease	Chylous ascites
Acute submassive hepatic necrosis	Myxedema
Widespread metastatic cancer in the liver	Eosinophilic gastroenteritis
Portal vein occlusion	Nephrogenous ascites

showed slight cardiomegaly with 1+ prominence of the interstitial markings (Figure 4). An electrocardiogram showed no abnormalities except for minor ST segment changes attributed to digitalis. Paracentesis disclosed the following: clear straw-colored ascites with 250 leukocytes per cu mm, with a differential count of 91 percent mononuclear cells, 9 percent polymorphonuclear cells and no erythrocytes; albumin 2.7 and globulin 2.5 grams per dl; LDH 87 and amylase less than 80 units per liter.

A technetium 99m sulfur colloid liver-spleen scan showed a diffusely enlarged liver measuring 18 cm in the midclavicular line with slightly diminished colloid uptake in the liver and mild redistribution of colloid activity to the spleen and bone marrow. The spleen was normal in size.

Serum thyroid-stimulating hormone, thyroxine and tri-iodothyronine values were normal. Twenty-four-hour urine sodium level was 11 mEq per liter.

At this point, the reader may wish to pause for a few minutes to consider the potential causes of ascites fluid with these characteristics.

DR. REYNOLDS: The high protein content of the patient's ascitic fluid (5.2 grams per dl) suggested an exudative or inflammatory cause such as tuberculosis or malignancy. Dr. Hoefs will help interpret this finding.

JOHN C. HOEFS, MD:* I will discuss the value of the protein concentration of ascitic fluid in determining the cause of this condition. The causes can be divided into those with vascular outflow obstruction (transudative) and those *without* vascular outflow obstruction and *with* peritoneal membrane involvement (exudative) (Table 1).

*Assistant Professor of Medicine.

Several types of ascites do not fit easily into these categories (such as myxedema, chylous ascites and nephrogenous ascites) but are usually considered part of the exudative group. Early studies of ascites suggested that transudative and exudative causes had characteristic protein concentrations.[6,7] This was confirmed in larger surveys,[8-10] which found that the most common transudative process (chronic liver disease) typically had an ascites protein concentration of less than 2.5 grams per dl and most exudative processes (tuberculosis and peritoneal carcinomatosis) had a protein concentration of greater than 2.5 grams per dl. However, these criteria could not separate other transudative sources (cardiac, inferior vena cava block and Budd-Chiari syndrome) from exudative ones. Even ascites secondary to chronic liver disease can have a high protein content; the frequency of high-protein ascites has approached 20 percent in recent studies by Sampliner and Iber,[3] Boyer and colleagues[2] and Bar-Meir and associates.[4] Liver disease (transudative) may be the most common cause of high-protein ascites if these estimates are accurate. The overlap in ascites protein concentration noted in these studies led to the recommendation of 3.0 grams per dl as the dividing line between transudative and exudative processes, but the recent surveys of Boyer and colleagues[2] and Bar-Meir and associates[4] have not found either 2.5 or 3.0 grams per dl reliable diagnostically. The former group[2] recommended multiple criteria similar to those used to separate transudate from exudate in pleural fluid; the usefulness of these criteria awaits further evaluation.

The high protein concentration in ascitic fluid with transudative processes had led to a general disenchantment with the diagnostic value of this determination. This change of attitude was further supported by the recognition that low protein concentrations in ascites resulting from chronic liver disease would increase to above 3.0 grams per dl in most patients during diuresis[3] or albumin infusions.[11-13] Total body extracellular fluid and total body extracellular protein seemed more important determinants of the ascitic protein concentration than the cause of ascites in these studies. It can be concluded that the ascites protein concentration of itself is not an adequate diagnostic tool for separating transudative from exudative causes.

Another diagnostic approach is to consider the relationship between serum and ascites protein

concentrations rather than the latter concentration alone. Boyer and colleagues[2] found the ascites-to-serum ratio (Asc:S) of protein and LD helpful in diagnosis. However, the (Asc:S) ratio of protein is not specific and increases into the range seen in exudative causes of ascites when patients with liver disease undergo diuresis[5] or albumin infusion.[13] The only relatively stable factor during diuresis, albumin infusion or saline ingestion in chronic liver disease is the serum-to-ascites albumin concentration or oncotic pressure difference.[5,11-14] This gradient is calculated by subtracting the ascites albumin concentration from the serum albumin concentration $[(S\text{-}Asc)_A]$ on simultaneous specimens and is thought to be determined by portal vein pressure.[14,15] In a preliminary communication,[16] we reported a good correlation between portal vein pressure and the $(S\text{-}Asc)_A$ in patients with liver disease, confirming this relationship. James[15] and Giges and Kunkel[11] suggested the use of this gradient as an indirect estimate of portal vein pressure. Because exudative causes have a normal portal vein pressure and patients with transudative causes have an elevated portal vein pressure, this gradient from serum-to-ascites albumin concentration $[(S\text{-}Asc)_A]$ or oncotic pressure $[(S\text{-}Asc)_{OP}]$ contains much diagnostic potential. Giges and Kunkel[11] found a smaller $(S\text{-}Asc)_{OP}$ in patients with exudative sources of ascites than in those with transudative sources, supporting its diagnostic value. In our own experience, the $(S\text{-}Asc)_A$ is equal to or greater than 1.0 gram per dl in 97 percent of patients with chronic liver disease. Patients with ascites of exudative causes (primarily tuberculosis, peritoneal carcinomatosis and pancreatic ascites) have had a value of less than 1.0 gram per dl.

Analysis of data from the few other studies in the literature in which simultaneous ascites and serum albumin concentrations can be abstracted are tabulated in Table 2 and support the potential value of the $(S\text{-}Asc)_A$ in distinguishing ascites of different causes.[5,9,10,13,17,18] As can be seen in Table 2, the predictable difference between portal vein pressure and intra-abdominal pressure for each disease category is related to the serum-ascites albumin concentration gradient. The serum albumin concentration was variable but lowest in cirrhosis and highest in cardiac disease. In cirrhosis, the increase in serum albumin concentration during diuresis was accompanied by a pronounced increase in the protein concentration of the ascitic fluids. A normal serum albumin concentration, a low serum-ascites albumin concentration gradient, or both, were found in all groups with high-protein ascites. Although the serum albumin concentration may be decreased with malignancy, the narrow $(S\text{-}Asc)_A$ results in high-protein ascites. There was little overlap in the

TABLE 2.—*The Serum to Ascites Albumin Concentration Gradient With Cirrhosis, Cardiac Failure and Peritoneal Carcinomatosis**

Author and Reference	*Number of Patients*	*Serum Albumin (grams per dl)*	*Serum to Ascites Albumin Gradient (grams per dl)*	*Expected PVP-IAP Gradient*	*Total Ascitic Protein Concentration (grams per dl)*
Cirrhosis					
Spak[10]	23	2.19	1.83	Increased	1.02
Rovelstad[9]	26	1.86	1.48		1.36
Berendsohn[17]	27	1.89	1.61		1.16
Hoefs[5]	25†	2.36	1.80		1.20
	25‡	3.08	1.43		2.98
Hoefs[13]	10§	2.07	1.44		1.30
	10‖	3.26	1.94		2.44
Cardiac					
Spak[10]	13	3.24	1.56	Normal to increased	3.23
Witte[18] Acute	9	3.67	0.89		5.70
Chronic	3	3.14	1.84		2.80
Peritoneal carcinomatosis					
Spak[10]	86	2.53	0.59	Normal	3.97
Rovelstad[9]	40	2.15	0.45		3.39

PVP-IAP = portal vein pressure—intra-abdominal pressure

*The mean albumin concentrations (serum and ascites) and ascites total protein concentration are abstracted from six studies and listed along with the anticipated portal vein pressure to intra-abdominal pressure gradient.
†Early diuresis.
‡Late diuresis.
§Initial: before albumin infusion.
‖Final: after albumin infusion.

TABLE 3.—*Hemodynamic Findings*

Pressures (mm of mercury)		*Other Determinations*	
Right atrium	22	Cardiac index (L/min/m²)	2.4
Right ventricle	50/23	Heart rate	64.0
Pulmonary artery	45/22	Stroke index (ml/m²)	37.0
Pulmonary artery wedge	23	End-diastolic volume (ml/m²)	59.0
Left ventricle	130/25	Ejection fraction	0.79
Aorta	127/60		

$(S\text{-}Asc)_A$ between transudative and exudative processes regardless of the ascitic protein concentration. We conclude that an $(S\text{-}Asc)_A$ of less than 1.0 gram per dl on simultaneously obtained serum and ascites specimens indicates that portal hypertension is minimal or absent and that ascites results from a condition *other than portal hypertension.*

The $(S\text{-}Ase)_A$ tends to be relatively constant while ascites increases in patients with liver disease because liver blood flow is maintained despite a pronounced increase in intra-abdominal tension with maintenance of a stable portal vein pressure-intra-abdominal pressure gradient.[19]

Figure 5.—Neck vein distention at 30° elevation of head of the bed.

However, with cardiac ascites and inferior vena cava block above the hepatic veins, the portal vein pressure remains constant during ascites formation as the intra-abdominal pressure increases. Therefore, with massive or tense ascites the intra-abdominal pressure may increase to the point where the $(S\text{-}Asc)_A$ gradient is relatively small. Cardiac ascites is known to be high in protein concentration. This is explained by the relatively high serum protein concentration and the relatively low pressure difference between the portal vein and ascites when the abdomen fills with fluid and becomes tense.

The serum albumin concentration and ascites protein concentration for the various causes of ascites are listed in Table 2. The $(S\text{-}Asc)_A$ in

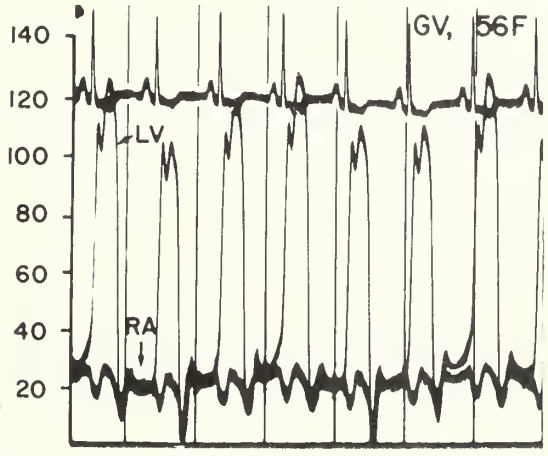


Figure 6.—Left ventricular (LV) and right atrial (RA) pressure tracings. Note the equalization of pressures in diastole.

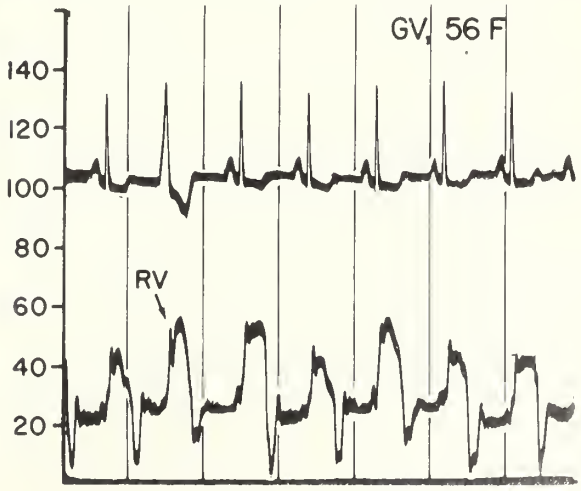


Figure 7.—Right ventricular (RV) pressure tracing showing the "dip-plateau" configuration (square root sign).

our patient pointed away from an exudative process despite the high ascites protein concentration, although the gradient of 1.0 grams per dl did not separate liver disease ascites from cardiac ascites.

We conclude that the ascites protein concentration does not separate transudative from exudative processes. An alternate approach is to assess the presence of portal hypertension indirectly from simultaneous measurement of ascites and serum albumin concentration (or oncotic pressure). Ascites associated with an $(S\text{-}Asc)_A$ gradient of less than 1.0 gram per dl is unlikely to be associated with portal hypertension, thereby eliminating chronic liver disease as the cause. Both exudative and transudative causes of ascites associated with increased vascular resistance distal to the hepatic veins (cardiac causes and inferior vena cava block above the hepatic veins) could have an $(S\text{-}Asc)_A$ determination of less than 1.0 gram per dl. However, an $(S\text{-}Asc)_A$ of less than 1.0 gram per dl is the rule for uncomplicated exudative causes[9,10] and the exception for cardiac ascites.[10,18] Thus, the $(S\text{-}Asc)_A$ would appear to be of great value in differentiating ascites of unknown causes and should be considered part of the routine evaluation of ascites.

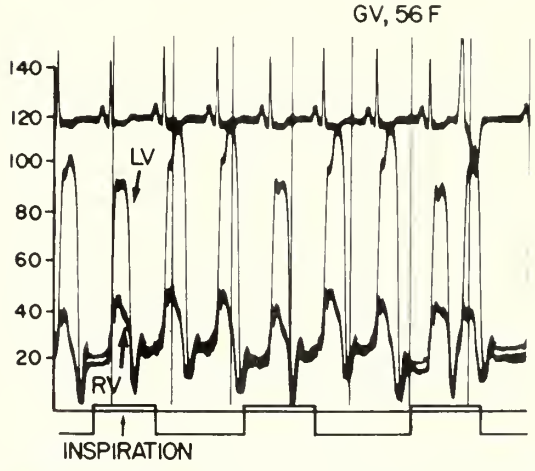


Figure 8.—Left ventricular (LV) and right ventricular (RV) pressure tracings. Note the equalization on diastole, square-root sign and drop in left ventricular systolic pressure during inspiration (paradoxical pulse).

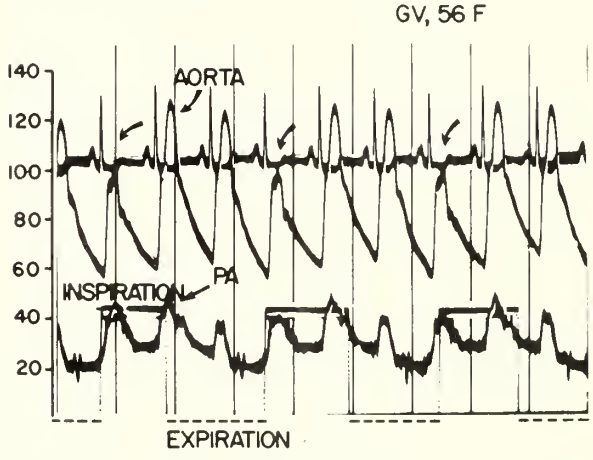


Figure 9.—Ascending aorta and pulmonary artery pressures showing a 20 to 30 mm of mercury paradoxical pulse (arrows).

DR. LINDSAY: Because of the consistent finding of neck vein distention on physical examination (Figure 5), constrictive pericarditis was considered, although neither paradoxical pulse nor the Kussmaul sign was detected. Cardiac catheterization was carried out on February 20, 1980.

Dr. Sanmarco will discuss the findings of cardiac catheterization.

MIGUEL E. SANMARCO, MD:* Cardiac catheterization showed findings that were typical of constrictive pericarditis. There was severe elevation and virtual equalization of the left ventricular diastolic, pulmonary arterial wedge, pulmonary arterial diastolic, right ventricular diastolic and right atrial pressures (see Table 3 and Figures 6 and 8).

An early dip-plateau configuration was noted in both the right and left ventricular pressure tracings (Figures 7 and 8), and the left ventricular and aortic pressures showed a 25 mm of mercury drop in inspiration. This paradoxical pulse is clearly seen in Figures 8 and 9.

Left ventricular function was normal as evidenced by normal values for end-diastolic volume and ejection fraction. Selective coronary arteriography detected a left dominant system with only minimal irregularities.

No pericardial calcification was seen; however, there was a substantial gap between the outer portion of the coronary arteries and the edge of the soft tissue density, suggesting increased pericardial thickness or pericardial effusion.

DR. LINDSAY: A tuberculin skin test was done and gave a positive reaction of 11 mm of induration at 48 hours. On March 3, 1980, resection of the pericardium was carried out, at which the pericardium was noted to be 3 to 4 mm in thickness.

Postoperatively, the patient did well. On March

*Associate Professor of Clinical Medicine.

25, serum urea nitrogen was 28 and creatinine 1.0 mg per dl. On a return visit in August, she reported resolution of exertional dyspnea. Neck vein distention was absent and she weighed 73 kg (160.6 lb).

REFERENCES

1. Light R, MacGregor M, Lucksinger P, et al: Pleural effusions: The diagnostic separation of transudates and exudates. Ann Intern Med 77:507-513, 1972

2. Boyer TD, Kahn AM, Reynolds TB: Diagnostic value of ascitic fluid lactic dehydrogenase, protein and WBC levels. Arch Intern Med 138:1103-1105, 1978

3. Sampliner RE, Iber FL: High protein ascites in patients with uncomplicated hepatic cirrhosis. Am J Med Sci 267:275-279, 1974

4. Bar-Meir S, Lerner E, Conn HO: Analysis of ascitic fluid in cirrhosis. Dig Dis Sci 24:136-144, 1979

5. Hoefs J: Transition to high protein cirrhotic ascites during diuresis (Abstract). Gastroenterology 73:27, 1977

6. Foord AG, Youngberg GE, Wetmore V: The chemistry and cytology of serous fluids. J Lab Clin Med 14:417-427, 1929

7. Gilligan DR, Volk MC, Blumgart HL: Observations on the chemical and physical relation between blood serum and body fluids—I. The nature of edema fluids and evidence regarding the mechanism of edema formation. J Clin Invest 13:365-381, 1934

8. Paddock FK: The diagnostic significance of serous fluids in disease. N Engl J Med 223:1010-1015, 1940

9. Rovelstad RA, Bartholomew LG, Cain JC, et al: I. The value of examination of ascitic fluid and blood for lipids and for proteins by electrophoresis. Gastroenterology 34:436-450, 1958

10. Spak I: On the clinical value of chemical analysis of ascites —A study of the main proteins and some enzymes in ascites of differing etiology. Acta Chir Scand 261:7-13, 1960

11. Patek AJ Jr, Mankin H, Colcher H, et al: The effects of intravenous injection of concentrated human serum albumin upon blood plasma, ascites and renal functions in three patients with cirrhosis of the liver. J Clin Invest 27:135-144, 1948

12. Mankin H, Lowell A: Osmotic factors influencing the formation of ascites in patients with cirrhosis of the liver. J Clin Invest 27:145-153, 1948

13. Hoefs J: Determinants of ascitic fluid protein in cirrhosis (Abstract). Clin Res 26:151, 1978

14. Giges B, Kunkel HG: Osmotic pressure measurements of serum and ascitic fluid in patients with cirrhosis of the liver. J Clin Invest 33:257-263, 1954

15. James AH: The mechanism of pleural and ascitic effusions with a suggested method for the indirect estimation of portal venous pressure. Clin Sci 8:292-313, 1949

16. Hoefs J: Portal pressure estimation by ascitic fluid analysis (Abstract). Gastroenterology 74:1168, 1978

17. Berendsohn S: Biochemical studies of the ascitic fluid in hepatic cirrhosis. Am J Dig Dis 7:160-166, 1962

18. Witte CL, Witte MH, Dumont AE, et al: Protein content in lymph and edema fluids in congestive heart failure. Circulation 40:623-630, 1969

19. Iwatsuki S, Reynolds TB: The effect of increased intra-abdominal pressure on hepatic hemodynamics in patients with chronic liver disease and portal hypertension. Gastroenterology 65:294-299, 1973

Emotional Handling of DES Patients

THE PHYSICIAN, especially the physician who prescribed these drugs, can minimize the regression in the mother most effectively by an approach that deals with the patient as one adult to another. The physician in his own style should state that he appreciates that the experience of knowing of DES exposure is a shock. He should acknowledge what took place by presenting the facts nonjudgmentally. All the physicians who gave this drug should call their patients in and should call the daughters in and say, "Look, we gave you DES and there's a possible problem with the offspring." The feeling should be expressed that the exposure, although worrisome, was given in good faith at a time when medical knowledge indicated that, in order to achieve the pregnancy or in order to hold the pregnancy, this drug was given as an accepted form of medical treatment. Daughters should be approached in the same way. Several of the methods that we do not feel help this whole situation in the daughters are statements such as these: "I'll take care of everything." This infantilizes the woman at a time when she does not need to feel increased dependence. She needs to feel more independent and self-sufficient at this time; "Everything will be OK"—this denies the impact of the news and gives her reassurance that may not be true; it may be premature to say that and it gives her the feeling that she is not being taken seriously and she is being lied to, especially in the face of widespread flood of news on the subject on television and in magazines. "Be quiet, stop crying, take a tranquilizer"—this sort of authoritarian approach will tend to create more anger. . . . And then, "I'll do anything to make it up to you"—and this is generally said by the doctor who is overcome by guilt and blames himself for giving the drug, and as a consequence becomes oversolicitous and overinvolved. Both doctor and patient may lose the sense of what can be done effectively in this sort of a situation.

—LOUIS BURKE, MD, *Boston*

Extracted from *Audio-Digest Obstetrics and Gynecology*, Vol. 28, No. 3, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1577 East Chevy Chase Drive, Glendale, CA 91206.

Refer to: Fitzgerald F: The great imitator, syphilis—Medical Staff Conference, University of California, San Francisco. West J Med 134:424-432, May 1981

The Great Imitator, Syphilis

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr, Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR. TIERNEY:* *The topic of this medical staff conference is the "great imitator," syphilis. Dr. Faith Fitzgerald, a University of California, San Francisco, alumna who has recently returned to California after a two-year absence, will discuss this disease of increasing importance.*

DR. FITZGERALD:† Between the 15th and 17th centuries, waves of pestilence swept Europe, decimating populations. The Black Death, bubonic plague, persists today but only in pockets. Typhus and typhoid have been largely eliminated by modern hygiene. Smallpox is, at last, a conquered disease. But greatpox, syphilis (so called because it was so much more dreadful than smallpox), is still epidemic among us.

Apocrypha has it that the sailors of Columbus brought gonorrhea to the New World and returned with syphilis to the Old. As in much early colonial trade, Europe got more than it gave.

The history of syphilis is a complex drama involving the rise and fall of kings, changing governments and devastating wars. The final act was to have been played in 1943, with the general introduction of penicillin. It was a "magic bullet"; cases of reported syphilis plummeted. The words "and syphilology" were dropped from the title of the *AMA Archives of Dermatology and Syphilology*. By the mid-1950's hospitals were no longer required to do routine admission serological tests for syphilis to become accredited. A generation of physicians were trained without seeing syphilis in all its protean manifestations. It was no longer the case, as it had been in Osler's time, that to know syphilis in its many manifestations and variations was to know clinical medicine.[1]

But syphilis flourished in neglect. Its resurrection was abetted by increasing promiscuity, a relatively simple therapy and a loss of detective diagnostic skill. Because syphilis had been "conquered," the federal government withdrew funding for US Public Health Service (USPHS) epidemiologic studies and case finding.[2]

In the early 1970's there were 23,000 cases of infectious syphilis per year reported to the USPHS. A conservative estimate has it that for every case reported, nine are not. This implies almost a quarter of a million new cases of syphilis per year in the United States.[3] There is still a great deal of syphilis for primary physicians to recognize, understand and treat.

Pathophysiology

Syphilis may have lessons to teach us in this modern immunologic era of medicine. Consider this most unusual infectious disease: An organism, the delicate spirochete *Treponema pallidum*, is no longer than a red blood cell. It is exquisitely sensitive to drying, heat and air. Yet it can infect

*Lawrence M. Tierney, Jr, MD, Associate Professor of Medicine; Assistant Chief, Medical Service, Veterans Administration Medical Center, San Francisco.

†Faith Fitzgerald, MD, Associate Professor of Medicine; Associate Dean for Student and Curricular Affairs, University of California, Davis, School of Medicine.

ABBREVIATIONS USED IN TEXT

FTA-ABS = fluorescent treponemal antibody absorption (test)
TPI = *Treponema pallidum* immobilization (test)

a human being anytime from the fourth month of intrauterine life to old age. It may affect any system and can remain destructive for the victim's entire lifetime. Or it may lie dormant for a quarter century or more, living in harmless parasitism with its host.

At its worst, it is a prolonged infectious polyvasculitis with immunopathologic overlay; at best, it is an inconvenient or embarrassing blood test result.

In the overwhelming majority of cases, the disease is transmitted by sexual activity. Transmission of the treponeme can occur through mucous membranes, minutely abraded skin or, some believe, by way of normal hair follicles. Entering through the dermis, the spirochetes seed rapidly into the lymphatics and from there enter the bloodstream to disseminate throughout the body. Invading the perivascular lymphatics of multiple organs, the treponemes stimulate a cellular inflammatory response to granulomata formation and proliferation in the intima of the vasa vasorum. The resulting decrease or loss of blood supply by tissues served by the injured vessels may lead to necrosis. Eventually, the acute inflammation is replaced by fibrous scar tissue.

T pallidum organisms may episodically, in the early stages of disease, break out again as spirochetemia. Or they may assume an intracellular sequestration in multiple tissues, protected by the cell, some think, from antibodies and antibacterial agents.[4]

The antibody response to the treponemes may be itself immunopathologic. Immune-deposit disease in syphilis so far has been documented in the kidneys.[5-7]

In later stages, tissue hypersensitivity to *T pallidum* may become prominent, including proliferative fibrosis with hypertrophic masses, reactive tissue and necrosis—that is, formation of gummata.

Stages of Syphilis

Beginning in 1891, Boeck in Oslo studied 2,000 patients with untreated syphilis to determine the natural course of the disease. Studies of this population have continued to 1955[8] (Figure 1). The various stages of syphilis are discussed below (see Table 1).

Acquired Syphilis

Primary. The cardinal feature of the primary stage is the chancre, occurring at the site of inoculation within three months of the exposure. Most chancres begin as papules, then erode and become ulcerative. They are painless, indolent, punched-out lesions which have a scanty yellow discharge. They teem with spirochetes and are highly infectious. They may appear anywhere, although 95 percent are genital. They have been noted to occur in or around the mouth, anus, breast, rectum, cervix and colostomy stoma. Untreated, they heal spontaneously.

Secondary. Generally this stage is clinically manifest within six months of exposure. The chancre or chancres may still be present but are usually healing. This stage has protean manifestations, but four major syndromes have been seen: (1) a constitutional, *flu*-like illness; (2)

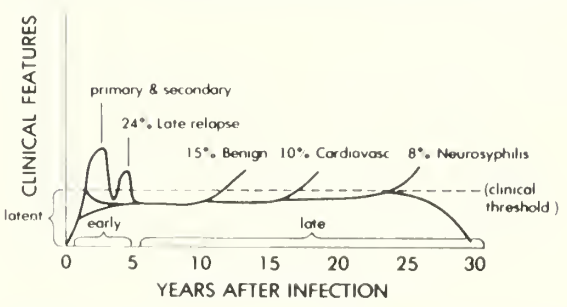


Figure 1.—Results of studies of the course of untreated syphilis in 2,000 patients.

TABLE 1.—*The Stages of Syphilis*

ACQUIRED SYPHILIS
Primary
Secondary
Latent
  Early latent
  Late latent
Tertiary
  Late benign syphilis
  Cardiovascular syphilis
  Neurosyphilis
    Meningovascular syphilis
    Aseptic meningitis
    Tabes dorsalis
      Preataxic
      Ataxic
      Paralytic
    General paresis of the insane
    Latent neurosyphilis
CONGENITAL SYPHILIS

generalized lymphadenopathy with or without splenomegaly; (3) rash, involving skin and mucous membranes, and (4) visceral involvement, such as hepatitis, nephritis, osteitis or gastritis.

The secondary stage is also infectious and, like the primary, will resolve without therapy.

Latent. Latent syphilis is hidden. By definition, there are no clinical manifestations.

Early latent is that period, generally two to four years from infection, during which spontaneous clinical relapse may occur, with resumption of spirochetemia and, usually, a secondary lues-like condition. During the four years following inoculation, the victim remains an epidemiologic threat because secondary lues is infectious. In almost a quarter of untreated patients this clinical recrudescence will occur.

Late latent is that stage of the disease after the fourth year from infection when the victim is no longer contagious but remains host to living treponemes.

In two thirds of untreated people, spirochetes and host will live amicably together until the patient dies of other causes. In about a third, however, the organism will continue to act upon the host to cause a variety of mischief—or, tertiary syphilis.[8-10]

Tertiary. Late benign syphilis occurs in about 15 percent of untreated victims. Gummata are its cardinal feature. A gumma seems to represent a proliferative reaction in which, though the patient appears to be in a latent state, there is chronically progressive inflammation and fibrosis. This may, depending on the organ involved, leave such severe scarring as to result in a pronounced disturbance of the affected tissues.

A gumma may undergo central necrosis, with breakthrough of the wall of the lesion, which then drains by way of one or more sinuses. Any tissue may be involved but the most frequently affected are bone, skin and upper respiratory tract.

Cardiovascular syphilis complicates the lives of about 10 percent of untreated sufferers. Osler[11] described the basic lesion of all syphilis in all stages and all organs as an endarteritis. It is within this category of tertiary lues that the truth of his observation is most evident. The basic lesion of cardiovascular syphilis is aortitis, with its pathological potential for aortic insufficiency, coronary vessel osteitis and ischemia, and the highly questionable entity of infective myocarditis.

Neurosyphilis affects some 8 percent of untreated persons. The classic manifestations of this late-stage involvement are tabes dorsalis and the general paresis of the insane. Active meningovascular syphilis is more commonly associated with secondary than with tertiary involvement.

Congenital Syphilis

A child born to a syphilitic mother may acquire the disease by transplacental transmission of *T pallidum.* Because the organism does not cross the placental barrier until the 16th to 19th week, early detection and therapy of the pregnant woman is effective.[12,13]

In untreated women, 25 percent of infected infants die in utero. Another 25 percent will die shortly after birth. In about 40 percent of the infants that survive—if untreated—symptomatic syphilis will occur, with developmental retardation, ocular, dental, neurological, bony, articular or visceral lesions all possible.[14]

Review of Systems

It has been said that syphilis, the great imitator, can look like anything. But if that is true, a clinician can have no discrete reason to suspect syphilis in any single circumstance. It must, then, be kept as a differential diagnosis to be considered in almost all cases. To illustrate this, it is useful to approach the disease from the point of view of systems, as one would do in ordinary history and physical examination, rather than reviewing the constellation of symptoms and signs in each stage; the latter all tend to merge and cross over anyway.

General

Puniness and growth retardation are features of congenital lues. Fever may accompany any stage of the disease but is most prominent in the malaise of secondary lues. It may be mild and continuous or, in its most remarkable form, paroxysmal, with spikes up to 40.6°C (105°F). Fever may persist for months, and syphilis must be part of the differential diagnosis in evaluation of fevers of unknown origin. Loss of weight, anemia, lymphocytosis and elevated erythrocyte sedimentation rate may be part of secondary syphilis. In the later stages, constitutional symptoms may be in consequence of the compromise of specific organs, as in the fatigue of luetic aortic insufficiency.

Nodes

Nodes neighboring the primary chancre may enlarge, growing hard and nontender. A more generalized lymphadenopathy is common in sec-

ondary syphilis, with pronounced involvement of epitrochlear and posterior cervical nodes. These enlarged nodes are rubbery and painless. Abdominal examination may show splenomegaly in this stage, and the lymphadenopathy may be so impressive as to be mistaken for mononucleosis—which secondary syphilis much resembles. More serious errors have been made as in the several reported instances in which patients narrowly escaped total nodal irradiation for putative Hodgkin disease, a misdiagnosis of their secondary lues.[15,16]

Skin

It is the skin that is the great mirror of luetic involvement and the organ on which we rely most for the diagnosis of syphilis. However, it may also be the most deceptive because it is in this area—even more than elsewhere—that the great imitator justifies its reputation for deceit.

In addition to the already described chancres of primary disease, cutaneous lesions are most common in the secondary stages of the disease. *Macular syphilid,* or syphilitic roseola, is most prominent on trunk and arms, often sparing the face. The symmetrically arranged macules are reddish-brown, persist for one to two weeks and may undergo multiple relapses. *Papular syphilid* may look like acne; a *pustular* rash resembles smallpox, or a *squamous syphilid* looks like psoriasis.

While syphilitic rashes may look like a variety of skin diseases, they have certain characteristics in common. They are often generalized, painless and nonpruritic and have a predilection for the palms and soles. The lesions are more commonly discrete than confluent and are sharply demarcated; and, like a reverse bull's-eye, the color becomes more intense as one proceeds from periphery to center.

Mucous patches are found in most areas of skin, such as perineum, groin or angle of mouth. They are flat, warty outgrowths with well-defined margins and surfaces covered with greyish secretions. They are highly infectious.

Gummata may affect any portion of the skin and leave scars as they involute or create ulcers as they break down. Because caseation occurs, gummata may be mistaken for tuberculosis.

Condylomata lata are highly infectious hypertrophied papillae of the perianal or perivulvar skin. They must be distinguished from the more common, virally induced condylomata acuminata.

Patchy alopecia or general thinning of the hair may occur in acquired lues, and the hair of head or eyebrows may fall out in the congenital form of the disease.

Syphilitic onycholysis is rare in other than congenital lues, though the nails may fall out entirely in severe secondary syphilis.

Head

Frontal, maxillary and mandibular bossing from periostitis of the skull are classic features of congenital lues. The saddle nose, with snuffles, of congenital disease occurs when syphilitic perichondritis erodes and collapses the nasal septum. The nose is also a favored spot for gummata.

Ears

Deafness may occur early in congenital lues, but has been reported to present as a Meniere-like condition in young adulthood[10] or from isolated VIII nerve failure in later neurosyphilis.

Mouth

In the oral cavity, the examiner may see chancres, glossitis, mucous patches, gummata, pharyngitis and palatal perforation from periostitis or the gummata. Hutchinson teeth (screwdriver-shaped secondary incisors) and mulberry molars (with supernumerary or defective cusps) are classic features of congenital disease.

Eyes

Ocular lesions include interstitial keratitis, iritis (occurs mostly in secondary syphilis, affecting one eye before the other, generally three to six months after the chancre), choritis and retinitis. The pupillary changes of tabes dorsalis are easy to remember: The Argyll-Robertson pupil may accommodate but does not react to light. Blindness may be a consequence of either optic nerve damage or inflammatory changes in other structures of the eye. Optic atrophy, ptosis and ophthalmoplegias have all been reported.

Neck

Gummata may involve the larynx, leading to misdiagnosis as cancer or tuberculosis. More urgently, such a mass may cause scarring and stridor. The hoarse "syphilitic cry" of congenital lues is probably due to laryngeal involvement.[9]

Breasts

Osler mentions syphilitic mastitis, with unilateral chronic diffuse induration or local nodules.[11] Axillary nodes may be involved, and the differ-

ential diagnosis from cancer of the breast may be difficult.

Chest

A gumma may involve the trachea, with bronchial dilatation below the lesion. Symptoms are those of obstruction, with dyspnea, stridor, cough and prolongation of inspiration. Rarely, tracheoesophageal fistulas may occur. Syphilitic pneumonia has been reported in congenital lues. Gummatous disease of the lungs, which is very uncommon, may resemble tuberculosis or fibrotic lung disease.[9]

Heart

Syphilitic endocarditis has not been described, though a nonbacterial thrombotic (marantic) endocarditis may coexist. Syphilitic myocarditis has been suspected on the basis of clinical findings, electrocardiogram and response to therapy during the spirochetemic phases of early lues. Still, this disease entity remains very much in doubt.[9]

Gummatous myocarditis, though very rare, has been recognized. Most gummata are in the left ventricular wall and may be associated with bundle branch block on electrocardiogram. Interventricular septal gumma may cause complete heart block[17] and, most uncommonly, a gumma may obstruct one or more coronary ostia.

Syphilitic aortitis is the basic and most frequent lesion of tertiary lues. During the spirochetemia of early disease, treponemes invade the aortic wall, probably by way of the vasa vasorum. An obliterating endarteritis follows, generally in the first portion of the aortic arch. Diffuse dilation or saccular aneurysm results. Dilatation of the aortic root separates the valve leaflets, with resultant aortic insufficiency. Inflammation of the wall may extend to involve the coronary ostia. Should they become occluded, myocardial ischemia or infarct may follow.

Symptoms may also arise from the simple mass effect of the aneurysm, which may compromise any of the mediastinal structures, including the trachea, bronchi, lungs, esophagus, vagus, cervical sympathetic nerves or the recurrent laryngeal nerve. The pulsatile mass may erode through adjacent ribs or spine. These aneurysms do not dissect, but they may rupture.

Abdominal aortic aneurysms are about a tenth as frequent as thoracic ones, and those of syphilitic origin are characteristically above the level of the renal arteries, in contrast to aneurysms of atherosclerotic origin, which are generally at or below this level. The syphilitic aneurysm may lie high under the diaphragm.[18]

Gastrointestinal

Hepatosplenomegaly is a common associate of congenital lues. The liver shows fibrosis and large numbers of spirochetes. Clinical jaundice, hepatomegaly with tenderness and increased levels of transaminase with a disproportionate rise in alkaline phosphatase, are the hallmarks of the syphilitic hepatitis of the secondary stage of disease. A liver biopsy specimen in syphilitic hepatitis will show portal inflammation, polymorphonuclear leukocytes surrounding bile ducts and necrotic areas extending from portal triads to central veins. Whether the spirochetes themselves can be seen in the liver tissue is a subject of dispute. Hepatic gummata may occur in tertiary disease and, with necrosis and scarring, lead to the classic hobnail liver of late syphilis.[11,19,20]

Acute esophagitis and erosive syphilitic gastritis may occur, the latter involving pain, vomiting, weight loss and hemorrhagic inflammation of the stomach on endoscopy. *T pallidum* may be demonstrated in biopsy material obtained from the gastric mucosa.[21]

Gummata of the esophagus may be mistaken for esophageal carcinoma, or the great imitator may present as pyloric obstruction, linitis plastica, or another intra-abdominal gummatous mass. Osler mentions the possibility of pancreatitis and jejunitis from syphilis. If these are luetic entities, they are rare.[11]

Rectal lues may manifest as chancres, and, as these are sometimes multiple, they may appear as a condition resembling ulcerative colitis, especially in homosexual men.[22]

Gummata should remain in the differential diagnosis of adenocarcinoma of the colon.

Genitourinary

In addition to genital chancres, the urinary tract has been variously involved by syphilitic lesions. Clinically, the most common manifestation of renal involvement is mild proteinuria, which may occur in secondary lues. A full-blown nephrotic syndrome accompanies secondary syphilis in some cases.[5] IgG immune complexes—treponemal antigen and antibody reactions—can be shown along the glomerular basement membrane.[6,7] The nephrosis remits with either treponemocidal therapy or the simple passage of time. Hemorrhagic

nephritis, indistinguishable on biopsy from that classically associated with poststreptococcal glomerulonephritis, is an uncommon but very serious complication which may progress to azotemia and death.[5] Paroxysmal cold hemoglobinuria may occur with congenital or acquired lues.[23] Muscle cramps, headache, fever and hemoglobinuria precipitated by cold will, in this case, respond to antisyphilitic therapy.

Prostatic and bladder gummata are rare and syphilitic orchitis rarer still. A neurogenic bladder may occur as a feature of neurosyphilis.

Extremities

Arthritis may occur at any stage of syphilis and may be so acute as to be mistaken for rheumatic fever. Or it may be chronic, with neuropathic painless destruction of joints. Arthritis of any sort is usually symmetrical.[13,14]

The Clutton joint of congenital lues involves hydrarthrosis, frequently bilateral, secondary to syphilitic synovitis with involvement of bone or cartilage. The Charcot joint of tertiary syphilis is neuropathic, that is, painless, with thickened synovium and cartilagenous injury. Most frequent in the knees, it may occur in the ankles or lumbar spine as well.

Bony lesions are part of both congenital and acquired lues. Periostitis, perichondritis, sclerosing osteitis, lytic lesions, gummata and bursitis have all been seen. Almost any bone, including the axial skeleton, may be involved.[24]

It is periostitis of the tibiae in congenital lues that produces the peculiar conformation called "sabre shins."

Osler noted syphilitic myositis in gastrocnemius and sternocleidomastoid muscles. On histological section, an affected muscle specimen shows vasculitis and interstitial myostis.[11]

Central Nervous System

The central nervous system may be involved in any stage of syphilis. There are four cardinal clinical categories.

Meningovascular syphilis is a manifestation of early lues, occurring within the first four years after primary infection. It presents as an aseptic meningitis, with headache, irritability and mental fatigue. Ocular features are common, often with remarkable variation from time to time. Pupils may be unequal or irregular and, although abnormal pupils have been noted in most patients with neurosyphilis, true Argyll-Robertson pupils are rare.[25] Ptosis, extraocular muscle palsies and optic neuritis have all been described.[11,26] Sudden, violent delirium, changes of character, prolonged stupor or coma, convulsions and major vascular occlusive events may complicate the picture. Studies of cerebrospinal fluid commonly show a positive VDRL result, increased protein and pleocytosis. A milder, transient aseptic meningitis sometimes accompanies secondary syphilis.

Tabes dorsalis is a neuropathy of late syphilis, in which there is degeneration of the root fibers of the posterior columns, spinal ganglia, cranial and peripheral nerves. There are three stages as follows: (1) in the *preataxic* stage, tabetic crises may occur involving lightning pains of the legs and trunk that last one to two seconds and follow the path of the dorsal nerve roots. Loss of pain and temperature sensation are concurrent. Ocular neuropathies, bladder symptoms, loss of deep tendon reflexes, deafness and paralysis of the vocal cords may follow. (2) The *ataxic* stage of tabes occurs when afferent impulses are lost, leading to incoordination and muscle hypotonia. Visceral crises, akin to pain crises, sometimes occur in this stage; gastric crises include severe epigastric pain, nausea, vomiting, hematemesis and, sometimes, death. The blood pressure may be very high, and the condition has been said to be associated with mesenteric vasospasm. Laryngeal crises may lead to sudden death; and even uncontrollable sneezing fits, the nasal crises, have been said to be tabetic in origin.[27] (3) After many years, the *paralytic stage* supervenes. The patient becomes bedridden and paralyzed, eventually dying of infection.

General paresis of the insane is a chronic luetic meningoencephalitis characterized by mental changes, dementia and paralysis. Irritability, changes in character, tremor, seizures, eye changes and hemicranial headaches may precede a hypomanic phase during which delusions of grandeur govern. Speech eventually becomes slurred, with syncope and paralysis thereafter. Death may occur during seizures, or a chronic dementia may persist for years.

Latent neurosyphilis has no signs or symptoms, but the cerebrospinal fluid has a positive VDRL.

In the modern era, classic tabes and general paresis are rare and are being replaced by atypical and in-between forms.[26] The nontreponemal serological tests for syphilis may be negative in as many as 40 percent of patients with neurosyphilis,[28] and the assumption that the serum fluores-

cent treponemal antibody absorption (FTA-ABS) test in serum is always positive has not held up.[29] For general purposes, however, a positive cerebrospinal fluid VDRL defines neurosyphilis, while cerebrospinal fluid pleocytosis and elevated protein level define its activity.

Laboratory Diagnosis

The laboratory tests for syphilis may be simple or confusing, depending on one's approach. Though there are any number of serological tests, the most commonly used study is the VDRL, the most sensitive is the FTA-ABS and the most specific is the *Treponema pallidum* immobilization test.

VDRL stands for Veneral Disease Research Laboratory and is a flocculation test that depends on the cross-reactivity of antitreponemal antibodies in the serum of the victim to a cardiolipin extract from cow's heart. It is easy and cheap and, thus, may be used for screening large numbers of patients.

In primary syphilis, about 25 percent of patients will have a positive VDRL test within the first week of the appearance of a chancre, 50 percent in the second week and 75 percent in the third week following infection.[2]

In secondary syphilis, close to 100 percent of VDRL tests are positive.

One must be careful in congenital lues, as the VDRL—an IgG function—measured in the first three postnatal months is that of the mother, not the child.

With therapy, about 25 percent of patients treated within four years will remain serofast; 75 percent will become serofast if treated later, but titers may decline, providing useful information about the adequacy of treatment.[30]

In neurosyphilis, 50 percent to 75 percent of victims will have reactive serum VDRL tests and almost 100 percent will have reactive serum FTA-ABS tests.[26] As few as 57 percent will have reactive cerebrospinal fluid VDRL tests,[26] but the value of FTA-ABS tests in cerebrospinal fluid remains in doubt.[31]

Biological false-positive VDRL tests may occur in a number of circumstances as listed in Table 2. The titer of a biological false-positive result is generally 1:4 or less. However, in one study of patients with biological false-positive results persisting for more than six months, about half of them turned out to have syphilis.[32]

FTA-ABS is the fluorescent treponemal antibody-absorption test, in which serum from the patient is applied to a slide on which *T pallidum* organisms have been dried. Globulin antibodies in the victim's serum adhere to the treponemes. Fluorescein-tagged antiglobulin antibodies are overlaid on the slide. The globulin on the treponemes binds the tagged antiglobulin and the slide is then read. To increase specificity, the test serum is pretreated with absorption to nonluetic treponemes that remove antibodies nonpathogenic to spirochetes.

TABLE 2.—*Biological False-Positive VDRL Tests*

Acute
Viral infections: herpes, mononucleosis, hepatitis
Lymphogranuloma venereum
Vaccinations
Immunizations
Chronic
Age
Heroin addiction
Leprosy
Malaria
Collagen disease
Lymphoma
Familial
Nonvenereal treponemes
Yaws
Pinta
Bejel
Passive reaginemia
Placental transfer

False-positive tests have been shown in systemic lupus, rheumatoid arthritis, lymphosarcoma, alcoholic cirrhosis and pregnancy.[32-35] It has been said that there are morphological differences between false and true positives in systemic lupus, with false results showing beading of the fluorescein tagging on the treponeme rather than linear deposition.[35]

The FTA-ABS is the most sensitive of all tests, being 75 percent positive in the earliest lues and close to 100 percent persisting thereafter. Only the very earliest therapy of seronegative (that is, VDRL-negative) primary syphilis will cause the FTA-ABS, in about 75 percent of those so treated, to revert to negative.[36]

The TPI (*Treponema pallidum* immobilization) test is done by adding patient serum (potentially containing antibody) and complement to a suspension of living treponemes extracted from rabbit testes. The test is run under a dark-field microscope and scored for whether immobilization of the organism occurs. Antibiotic drugs taken by the patient will invalidate the test, which is technically difficult under the best of circumstances. It is far less sensitive than the FTA-ABS test but far more specific than any other laboratory investigation

short of staining the organism in tissue. It is not available in most hospitals but can be obtained through the Communicable Disease Center, Atlanta.

Diagnosis of Suspected Lues

After a complete history and physical examination, dark-field microscopic examination should be done on all suspected lesions. It is, however, a waste of time to do a dark-field study on lesions in the mouth, as normal oral treponemes may be present. If the VDRL test is insufficiently convincing for diagnosis, an FTA-ABS test should be done. A suggested approach is outlined in Figure 2.

Therapy

If syphilis is diagnosed, the nature of therapy depends on the stage of the disease (Table 3).

Studies show that a total dose of 6 to 9 million units of parenteral penicillin G results in a satisfactory clinical response in about 90 percent of patients with neurosyphilis.[37] Because living treponemes have been shown in aqueous humor and the central nervous system following supposed ablative therapy, and because neurological signs may continue to progress even with apparently adequate therapy, some clinicians will hospitalize patients with neurosyphilis, especially if the victim is symptomatic or has not responded to initial therapy. In the latter case, one may wish to increase the total dose of aqueous penicillin G to 12 to 24 million units given intravenously each day for ten days. It has been proposed that the 9.6 million unit standard dose, though spirochetocidal in blood, does not achieve adequate therapeutic levels in the CSF.[38]

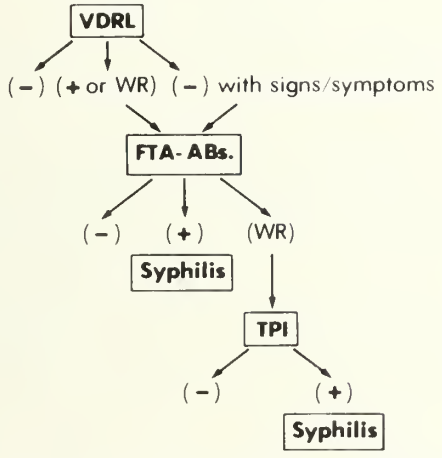


Figure 2.—Laboratory evaluation of suspected syphilis. (FTA-ABs = fluorescent treponemal antibody absorption [test]; TPI = *Treponema pallidum* immobilization [test]; VDRL = Venereal Disease Research Laboratory [test]; WR = weakly reactive.)

In case of syphilis of unknown duration, a cerebrospinal fluid VDRL test should be carried out if there are any symptoms suggestive of neurosyphilis because there may be a therapeutic difference. All patients should have repeat serological testing done 24 months after therapy. Careful follow-up is especially important in those treated with antibiotics other than penicillin, because the efficacy of these alternatives in late lues and, especially, in neurosyphilis is unproved. In a patient with established neurosyphilis, serological testing should continue for three years, with clinical and CSF examinations every six months.

Retreatment should be considered in the following situations: (1) when clinical signs or symptoms of syphilis persist or recur, (2) when there is a sustained fourfold increase in the titer of the VDRL test or (3) when an initially high titer for the VDRL test fails to show a fourfold decrease within a year.

The Jarish-Herxheimer reaction is so common

TABLE 3.—*Appropriate Therapy Depending on the Stage of Syphilis*

Stage	*Therapy*	*Serological Finding Without Therapy (Percent)*		
		FTA-ABS	*VDRL*	*TPI*
Congenital	50,000 units benzathine penicillin G/kg of body weight in single dose		↑ titers ×3 mos	
Acquired				
Primary (≤3 mos.)	2.4 million units benzathine penicillin G in single dose	85	25-75	55
Secondary (≤6 mos.)		99	97	94
Early latent (≤4 yrs.)	2.4 million units benzathine penicillin G every 10 days ×4 doses	95	74	94
Late latent (>4 yrs.)				
Late benign				
Cardiovascular				
Neurosyphilis	2.4 million units benzathine penicillin G every 10 days ×4 doses (see text)	95	74	94

FTA-ABS = fluorescent treponemal antibody absorption (test); TPI = *Treponema pallidum* immobilization (test)

an accompaniment of the therapy of syphilis that it deserves mention here. Nine out of ten patients with secondary and, to a lesser extent, other stages of syphilis will show a Jarish-Herxheimer reaction within several hours of their first dose of the antibiotic drug. The reaction is characterized by chills, fever, headache, muscle and joint pains. Skin lesions may become more prominent, more edematous and more brilliant in color. The reaction lasts several hours and does not recur following subsequent injections. It may be interpreted by the patient and unwary physician as an allergy to penicillin, and a careful history is required to distinguish between the two. The Jarish-Herxheimer reaction is thought to be due to the sudden release of large amounts of treponemal antigen, with subsequent antigen-antibody reaction in the host.

Summary

Syphilis, once thought a conquered disease, is still very much with us. Because many physicians are not familiar with its multitudinous manifestations and the changes in classic presentation induced by the ubiquity of antibiotics, syphilis remains a diagnostic and therapeutic challenge to the modern era. Osler was right.

REFERENCES

1. Osler W: Familiar Medical Quotations, 1st Ed. Boston, Little, Brown and Co, 1968, p 651

2. Miller JN, Nelson JR, Reisner RM, et al: Syphilis. Calif Med 115:47-60, Aug 1971

3. Lucas JB: The national venereal disease problem. Med Clinics N Am 56:2073-2086, 1972

4. Sykes JA, Miller JN: Intracellular location of Treponema pallidum (Nichols Strain) in the rabbit testis. Infect Immun 4: 307-314, 1971

5. Bhorade MS, Carag HB, Hwa JL, et al: Nephropathy of secondary syphilis. JAMA 216:1159-1166, 1971

6. Gamble CN, Reardan JB: Immunopathogenesis of syphilitic glomerulonephritis. N Engl J Med 292:449-454, 1975

7. O'Regan S, Fong JSC, deChadarevian J-P, et al: Treponemal antigens in congenital and acquired syphilitic nephritis. Ann Intern Med 85:325-327, 1976

8. Clark EG, Danbolt N: The Oslo study of the natural course of untreated syphilis. Med Clinics N Am 48:613-623, 1964

9. Kampmeier RN: The late manifestations of syphilis: skeletal, visceral and cardiovascular. Med Clinics N Am 48:667-697, 1964

10. Syphilis: A Synopsis, Public Health Service Publication No. 1660. US Dept of Health, Education, and Welfare, 1967

11. Osler W: Syphilis, *In* Osler's Principles and Practice of Medicine, Ed. XIII, revised by HA Christian. New York, D. Appleton-Century Co., Inc., 1938, pp 344-369

12. Holder WR, Knox JM: Syphilis in pregnancy. Med Clinics N Am 56:1151-1160, 1972

13. Curtis AC, Philpott OS Jr: Prenatal syphilis. Med Clinics N Am 48:707-719, 1964

14. Thomas EW: Syphilis: Its Course and Management. New York, Macmillan Co, 1949

15. Goffinet DR, Hoyt C, Eltringham JR: Secondary syphilis misdiagnosed as lymphoma. Calif Med 112:22-23, 1970

16. Nayeem SA, Bernhardt B: Syphilitic lymphadenopathy. JAMA 239:495, 1978

17. Wenstein A, Kampmeier RN, Harwood TR: Complete heart block due to syphilis. Arch Intern Med 100:90, 1957

18. Kampmeier RH: Aneurysm of the abdominal aorta: A study of 73 cases. Am J Med Sci 192:97, 1936

19. Sherlock S: The liver in secondary (early) syphilis. N Engl J Med 284:1437-1438, 1971

20. Baker AL, Kaplan MM, Wolfe HJ, et al: Liver disease associated with early syphilis. N Engl J Med 284:1422-1423, 1971

21. Sachar DB, Klein RS, Swerdlow F, et al: Erosive syphilitic gastritis: Darkfield and immunofluorescent diagnosis from biopsy specimen. Ann Intern Med 80:512-515, 1974

22. Nazemi MM, Musher DM, Schell RF, et al: Syphilitic proctitis in a homosexual. JAMA 231:389, 1975

23. Wintrobe MM: Paroxysmal (cold) hemoglobinuria, *In* Clinical Hematology, 6th Ed. Philadelphia, Lea & Febiger, 1967, pp 660-663

24. Dismukes WE, Delgado DG, Mallernee SV, et al: Destructive bone disease in early syphilis. JAMA 236:2646-2648, 1976

25. Syphilis, Public Health Service Publication No. 743. US Dept of Health, Education, and Welfare, 1961

26. Hooshmand H, Escobar MR, Kopf SW: Neurosyphilis—A study of 24 patients. JAMA 219:726-729, Feb 1972

27. Osler W: Tabes dorsalis, *In* Osler's Principles and Practice of Medicine, Ed. XIII, revised by HA Christian. New York, D. Appleton-Century Co. Inc, 1938, pp 1173-1187

28. Harner RE, Smith JL, Israel CW: The FTA-ABS test in late syphilis. JAMA 203:545-548, 1968

29. Deacon WE, Lucas JB, Price EV: Fluorescent treponemal antibody-absorption (FTA-ABS) test for syphilis. JAMA 198: 624-628, 1966

30. Fiumara NJ: Syphilis resurgent. Drug Therapy, Apr 1971, pp 47-49

31. Jaffe HW: The laboratory diagnosis of syphilis. Ann Intern Med 83:846-850, 1975

32. Tuffanelli DL, Wuepper KD, Bradford LL, et al: Fluorescent treponemal antibody absorption tests: Studies of false positive reactions to tests for syphilis. N Engl J Med 276:258-262, 1967

33. Mackey DM, Price EV, Knox JM, et al: Specificity of the FTA-ABS test for syphilis. JAMA 207:1683-1685, 1969

34. Sparling PF: Diagnosis and treatment of syphilis. N Engl J Med 284:642-652, 1971

35. Kraus SJ, Haserick JR, Lantz MM: Fluorescent treponemal antibody-absorption test reactions in lupus erythematosus. N Engl J Med 282:1287-1290, 1970

36. Schroeter AL, Lucas JB, Price EV, et al: Treatment for early syphilis and reactivity of serologic tests. JAMA 221:471-476, 1972

37. Center for Disease Control: Syphilis—Recommended treatment schedules, 1976. Ann Intern Med 85:94-96, 1976

38. Yoder FW: Penicillin treatment of neurosyphilis. JAMA 232:270-271, 1975

Important Advances in Clinical Medicine

Epitomes of Progress — Nuclear Medicine

The Scientific Board of the California Medical Association presents the following inventory of items of progress in nuclear medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in nuclear medicine which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Nuclear Medicine of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Meckel Diverticulum, Barrett Esophagus and Retained Gastric Antrum Syndrome

SCINTIGRAPHY using pertechnetate labeled with technetium 99m is a useful noninvasive diagnostic procedure for the localization of normal or ectopic gastric mucosa, as occurs in Meckel diverticulum, Barrett esophagus and retained gastric antrum after gastrectomy. Pertechnetate is a monovalent anion, as is chloride, and its mechanism of concentration appears to be similar. After administration of pertechnetate Tc 99m, gastric mucosa can be demonstrated with a conventional gamma camera technique as a hot spot.

Meckel diverticulum occurs in 1.5 percent to 3 percent of the general population, and in approximately 25 percent to 30 percent of these persons clinical symptoms will develop. Although ectopic gastric mucosa is found in less than 20 percent of all diverticula, it is present in nearly all cases associated with gastrointestinal bleeding. Use of barium contrast radiography or selective arteriography is often unsuccessful in establishing the diagnosis. In two combined studies using pertechnetate Tc 99m scans of 78 adults and 136 children, there were 50 true-positive, 137 true-negative, 12 false-positive and 15 false-negative test results. False-positive findings are frequently of surgical significance because they may actually indicate an abscess, appendicitis, peptic ulceration, hemangioma or intussusception. False-negative examination results occur in patients with insufficient gastric mucosa or necrosis of the diverticulum.

In Barrett esophagus, columnar gastric epithelium replaces the normal stratified squamous epithelium. The epithelium is usually located in the lower esophagus, occasionally in the midesophagus and rarely in the upper esophagus. Although the diagnosis is often made on the basis of clinical findings and a barium swallow study, the pertechnetate Tc 99m scan offers added specificity and delineates the extent of esophageal involvement.

Recurrent ulceration in patients following gastrectomies has multiple causes. If, in addition, high levels of circulating gastrin are found, Zollinger-Ellison syndrome or retained gastric antrum in the duodenal stump must be considered. Increased gastrin secretion is seen in the latter condition because the normal inhibitory effect of gastric acidity is absent. Because these two conditions are differentiated with difficulty, the pertechnetate Tc 99m scan is useful because only the retained gastric antrum syndrome will be associ-

ated with increased uptake of pertechnetate Tc 99m on scintigraphy.

CAROL S. MARCUS, MD
W. H. BLAHD, MD

REFERENCES

Berquist TH, Nolan NG, Stephens DH, et al: Specificity of ^{99m}Tc-pertechnetate in scintigraphic diagnosis of Meckel's diverticulum: Review of 100 cases. J Nucl Med 17:465-469, Jun 1976

Sailer JF, Janeway CM: Pertechnetate demonstration of a Barrett's esophagus involving the length of the esophagus (Letter). J Nucl Med 19:1366-1368, Dec 1978

Sciarretta G, Malaguti P, Turba E, et al: Retained gastric antrum syndrome diagnosed by ^{99m}Tc-pertechnetate scintiphotography in man: Hormonal and radioisotopic study of two cases. J Nucl Med 19:377-380, Apr 1978

Hepatobiliary Imaging by Radionuclide Scintigraphy

RADIONUCLIDE IMAGING of the hepatobiliary system has been substantially improved with the introduction of compounds tagged with technetium 99m. The two radioactive pharmaceutical agents most commonly used are the N-substituted iminodiacetic acid (IDA) derivatives HIDA (dimethyl-IDA) labeled with ^{99m}Tc and PIPIDA (para-isopropyl-IDA) labeled with ^{99m}Tc. These agents offer substantial advantages over the previously used agent rose bengal ^{131}I (8.1 days physical half-life), including a short six-hour physical half-life, better counting statistics and relatively low radiation dose to the patient.

The radionuclide is removed rapidly from the blood by the polygonal cells of the liver. The liver is visualized within 5 minutes, and within 15 to 30 minutes most of the radioactive material has been removed from the bloodstream and concentrated by the liver. The gallbladder is seen in 30 to 60 minutes, and radioactivity is identified in the gastrointestinal tract usually by the end of the first hour.

These agents are capable of visualizing the biliary system at bilirubin levels of up to 8 mg per dl; at higher levels (>10 mg per dl), PIPIDA ^{99m}Tc is the preferred agent. This technique has a considerable advantage over intravenous cholangiography, in which biliary visualization diminishes rapidly when the bilirubin level rises to 2 to 4 mg per dl. Also, it provides an ideal study medium for patients who are allergic to radiographic contrast media.

Radionuclide cholescintigraphy has considerably reduced the need for intravenous cholangiography in the diagnosis of acute cholecystitis because a normal study in effect excludes this diagnosis. In jaundiced patients, it can be used to distinguish biliary tract obstruction from hepatocellular disease. These agents are also useful in determining postoperative patency of biliary anastomoses, in evaluating defects seen on technetium 99m sulfur colloid liver scans and in evaluating suspected biliary atresia in infants.

An important advantage of cholescintigraphy over ultrasonography and computed tomography is that the former provides both physiological and anatomical measures of hepatobiliary diseases, whereas the latter two provide only anatomical information.

RAKHI RAM, MD
NORMAN POE, MD

REFERENCES

Cheng TH, Davis MA, Seltzer SE, et al: Evaluation of hepatobiliary imaging by radionuclide scintigraphy, ultrasonography and contrast cholangiography. Radiology 133:761-767, Dec 1979

Fonseca C, Greenberg D, Rosenthall L, et al: Assessment of the utility of gallbladder imaging with 99m Tc-IDA. Clin Med 3: 437-441, Nov 1978

Weissmann HS, Frank M, Rosenblatt R, et al: Cholescintigraphy, ultrasonography and computerized tomography in the evaluation of biliary tract disorders. Semin Nucl Med 9:22-35, Jan 1979

Serum Thyroglobulin Levels: Their Use in Monitoring Thyroid Carcinoma

THE DETERMINATION of serum thyroglobulin levels, a major thyroid protein prohormone and the site of synthesis of thyroid hormone, represents an important advance in monitoring the disease course of patients with differentiated thyroid carcinoma. With the recent development of commercial radioimmunoassay kits for serum thyroglobulin, the assay will be more widely available to clinicians. It must be emphasized that thyroglobulin is *not* the same entity as thyroxine-binding globulin, a major binder of thyroid hormone in the blood.

In patients with papillary, follicular or mixed papillary-follicular tumors who have had subtotal thyroidectomy and subsequent ablation with iodide I 131, serum levels of thyroglobulin will become low or undetectable several weeks after treatment. However, thyroglobulin levels will be elevated in patients with widely metastatic disease. The level of thyroglobulin may be a more sensitive indicator of the presence of recurrent disease than standard iodide I 131 metastatic scans. In some cases thyroglobulin levels will be abnormal, while no abnormal uptake of radioactive iodine is noted on imaging. Other advantages of the technique include the ability to do the assay while the patient is receiving thyroid replacement therapy. However, if levels are undetectable, the assay should be repeated after terminating replacement therapy. Because thyroglobulin antibodies interfere with the assay and may invalidate results, the patient's serum specimens should be screened for antibodies before measuring thyroglobulin levels.

Thyroglobulin levels are useful indicators in patients rendered athyrotic because detectable levels of thyroglobulin can be identified in persons without thyroid disease and elevated levels can be seen in patients with autoimmune disease of the thyroid. However, the level of thyroglobulin is of no value in the separation of benign from malignant thyroid nodules.

MARTIN A. SCHWARTZ, MD
W. H. BLAHD, MD

REFERENCES

Van Herle AJ, Vassart G, Dumont JE: Control of thyroglobulin synthesis and secretion. N Engl J Med 301:239-249, 307-314, Aug 2, 1979, Aug 9, 1979

Schlossberg AH, Jacobson JC, Ibbertson HK: Serum thyroglobulin in the diagnosis and management of thyroid carcinoma. Clin Endocrin 10:17-27, Jan 1979

Regional Cerebral Blood Flow

IN CONTRAST to the qualitative estimate of cerebral blood flow obtained with a routine brain scan, a more precise estimation of regional cerebral blood flow can be obtained using freely diffusible xenon 133 gas. The washout of the radioactive gas from the head is monitored using either one or several radiation detection probes to calculate cerebral blood flow. Xenon 133 may be injected into the internal carotid artery by way of catheter or peripherally into a vein, or it may be inhaled and passed into the bloodstream by way of the pulmonary capillaries. Although the amount of blood flow in grey matter is of greatest importance, the probes can measure radioactivity in white matter and, with intravenously given or inhaled xenon 133, in extracerebral tissues as well. To differentiate between these compartments, washout is monitored for at least ten minutes. The first portion of the biphasic washout curve is assumed to be produced by activity in the grey matter, with the second portion primarily produced by activity in the white matter and extracerebral tissue. Equations derived from the Fick principle are applied to the curve to calculate regional blood flow in both white and grey matter. Sources of error include scattered radiation from outside the probe field of view, an unknown contribution to the count rate from extracerebral tissues and the pronounced effect of the partition coefficient (or differential solubility in tissue) of ^{133}Xe, which may vary greatly in areas of abnormal tissue.

In spite of the sources of error, the procedure provides sufficient information to be useful in the diagnosis and follow-up after surgical treatment of cerebrovascular disease. It is also useful in conditions of low blood flow such as dementia and after severe head injuries as well as to show the response to ventricular shunting in normal pressure hydrocephalus.

Because of the value of quantitating cerebral blood flow, better methods of estimation are being sought. One involves use of krypton 81m, a gas with a 13-second half-life, to show arterial flow. Others use an emission computed tomographic scanner, with a positron-emitting radionuclide to demonstrate distribution of blood flow in the brain. As yet, these methods are confined to a few research centers.

NORAH MILNE, MD
KENNETH P. LYONS, MD

REFERENCES

Holman BL: Concepts and clinical utility of the measurement of cerebral blood flow. Semin Nucl Med 6:233-251, Jul 1976

Obrist WD, Thompson HK Jr, Wang HS, et al: Regional cerebral blood flow estimated by 133-xenon inhalation. Stroke 6:245-256, May-Jun 1975

Phelps ME: Emission computed tomography. Semin Nucl Med 7:337-365, Oct 1977

Melamed E, Lavy S, Bentin S, et al: Reduction in regional cerebral blood flow during normal aging in man. Stroke 11:31-35, Jan-Feb 1980

Adrenal Scintigraphy

IN 1970 iodocholesterol labeled with iodine 131 was introduced for scanning the adrenal glands. Since 1975 iodomethylnorcholesterol ^{131}I has been the agent of choice because of its higher organ-to-background ratio. Adrenal scintigraphy can be used to demonstrate adrenal structure and function in a manner similar to radioactive iodine scintigraphy being used for the thyroid gland. In more than 95 percent of cases of Cushing syndrome, the adrenal scan can differentiate between hyperplasia, carcinoma or adenoma. An autonomously functioning, unilateral, adrenal adenoma can be detected before the disease is evident clinically, even when plasma cortisol levels are still normal.

Adrenal scintigraphy is the most sensitive method for localizing hyperfunctioning adrenal remnants following bilateral adrenalectomy. Adrenal suppression with dexamethasone can be used to demonstrate aldosterone- or androgen-producing adenomas which appear as a unilateral increase in uptake. The specificity of suppression scans for lateralizing aldosterone-secreting tumors is 94 percent. The advantage of this method is the elimination of adrenal arteriography and venography particularly when the scan demonstrates unilateral pathology. These radioactive cholesterol agents do not concentrate in medullary tissue; therefore, the procedure is less sensitive

for pheochromocytomas which must be at least 2 cm in diameter and distort the cortical tissue before detection is possible.

Preliminary results of adrenal scanning indicate its potential benefit in low-renin essential hypertension. Patients with nonsuppressible adrenal glands responded well to spironolactone therapy; poor response to such therapy has been found with normal adrenal suppression.

Administration of corticosteroids will cause poor or absent adrenal uptake. Information about the patient's medication is important to avoid spurious interpretation of scan findings while the adrenal glands are being stimulated or suppressed in the course of endocrinologic evaluations.

ALADAR KABOK, MD
KENNETH P. LYONS, MD

REFERENCES

Sarkar SD, Cohen EL, Beierwaltes WH, et al: A new and superior adrenal imaging agent, ^{131}I-6beta-iodomethyl-19-nor-cholesterol (NP-59): Evaluation in humans. J Clin Endocrinol Metab 45:353-362, Aug 1977

Thrall JH, Freitas JE, Beierwaltes WH: Adrenal scintigraphy. Semin Nucl Med 8:23-41, Jan 1978

Miles JM, Wahner HW, Carpenter PC, et al: Adrenal scintiscanning with NP-59, a new radioiodinated cholesterol agent. Mayo Clin Proc 54:321-327, May 1979

Radionuclide Technique for Detection of Acute Gastrointestinal Bleeding

ONE OF THE most challenging problems faced by clinicians in testing patients with acute gastrointestinal bleeding is locating the exact site of the bleeding. While angiography and endoscopy are excellent procedures, they are invasive, require well-trained personnel and present some risk to the patient. Radionuclide studies are noninvasive and are more sensitive than angiography in the detection of the bleeding site. The study can be done in a patient's room with a mobile camera and is of particular value for a patient who is too ill to undergo invasive studies.

A new radionuclide technique employed in the detection of gastrointestinal bleeding uses erythrocytes labeled in vivo with stannous pyrosphosphate ^{99m}Tc. Images of the abdomen are obtained immediately and repeated for up to three to four hours or longer, as necessary. Usually it takes less than 30 minutes to detect an active bleeding site. An advantage of this technique is its ability to detect occult or intermittent bleeding over a 24-hour period. Such sites can be identified in patients when the rate of bleeding is as slow as 0.3 ml per minute.

Another radionuclide agent employed in the detection of gastrointestinal bleeding is technetium 99m sulfur colloid, which is given intravenously. The colloid is cleared rapidly by the reticuloendothelial system so that the fraction of injected radioactive colloid that extravasates at the bleeding site can be seen as a focal accumulation of activity.

RAKHI RAM, MD
NORMAN POE, MD

REFERENCES

Alavi A, Dann RW, Baum S, et al: Scintigraphic detection of acute gastrointestinal bleeding. Radiology 124:753-756, Sep 1977

Winzelberg GG, McKusick KA, Strauss HW, et al: Evaluation of gastrointestinal bleeding by red blood cells labeled in vivo with technetium-99m. J Nucl Med 20:1080-1086, Oct 1979

Leukocyte Labeling With ^{111}In Oxine for Acute Inflammatory Disease

BECAUSE LEUKOCYTES are involved in the pathological process of inflammation, the ability to label and subsequently image their distribution in the body has long been of interest to both nuclear physicians and clinicians. Recently, a new radioactive agent for labeling leukocytes, indium-111 8-hydroxy quinoline (^{111}In oxine), has been described. This compound labels an intracellular component of the leukocytes. Indium is not eluted after labeling of cells and does not appear to alter the cells' biological function, survival or distribution.

Leukocytes are obtained from a patient's peripheral blood specimen and labeled in vitro with ^{111}In oxine. The autologously labeled leukocytes are injected back into the patient and whole-body imaging carried out. Abnormal radioactivity is observed at sites of leukocyte accumulation, including inflammation and abscess. Because of the high degree of specificity for detecting lesions with inflammatory infiltrates, this technique has been successful both in the identification and localization of abscesses.

Gallium-67 citrate is the alternative radioactive pharmaceutical agent used to detect abscesses. Because it may concentrate in neoplasms and is excreted in the bowel, its use in the detection of abscesses may result in misinterpretation of findings.

Recent comparative studies favor the use of the ^{111}In technique for abscess detection and indicate that it is superior to ^{67}Ga scans. A diagnostic accuracy rate of 92 percent has been reported for ^{111}In oxine leukocyte scanning, comparing favorably with accuracies of 96 percent for computed tomography and 90 percent for ultrasonography.

The disadvantages of this technique include the

length and complexity of the labeling procedure and the limited availability and expense of the radionuclide. However, because of its potential diagnostic use, it is anticipated that this test will be more widely available in the future.

MYRA V. DRICKMAN, MD
JUDITH G. ROSE, MD

REFERENCES

Thakur ML, Coleman RE, Mayhall CG, et al: Preparation and evaluation of ^{111}In-labeled leukocytes as an abscess imaging agent in dogs. Radiology 119:731-732, Jun 1976

Doherty PW, Bushberg JT, Lipton MJ, et al: The use of indium-111-labeled leukocytes for abscess detection. Clin Nucl Med 3:108-110, Mar 1978

Knochel JQ, Koehler PR, Lee TG, et al: Diagnosis of abdominal abscesses with computed tomography, ultrasound, and ^{111}In leukocyte scans. Radiology 137:425-432, Nov 1980

Detection of Acute Myocardial Infarction by Pyrophosphate ^{99m}Tc Scintigraphy

SIX YEARS AGO the use of scintigraphy with pyrophosphate labeled with technetium 99m was introduced as a method to detect acute myocardial infarction (AMI). Subsequent experience has substantiated the initial reports of Bonte and Parkey, and a sensitivity in the range of 90 percent for detecting acute infarction has been observed. Ideally the study is done 36 to 48 hours after infarction has occurred, but positive studies have been reported during the first 24 hours. An early negative study should be followed up with a repeat test two to three days later.

Like most sensitive tests, this method is relatively nonspecific. For example, ventricular aneurysms, unstable angina, calcified valves and pericarditis have produced positive test results. Varying degrees of specificity can be attained, however, by grading the studies according to the pattern as well as the intensity of the activity in the myocardium. The measurement of 90 percent sensitivity for diagnosing AMI is based on a grading by intensity level as the only criterion for determining positive findings. If the pattern of cardiac activity is also graded as either diffuse throughout the myocardium or localized to a specific wall of the myocardium, then the sensitivity decreases but the specificity increases considerably. In a coronary care unit two thirds of the patients with AMI will have a localized pattern of activity on the scintigrams. The specificity of this finding is 95 percent. Over a fourth of the patients will have the highest intensity grade in addition to the localized pattern, and in these patients specificity will be 99 percent.

Myocardial scintigraphy using pyrophosphate ^{99m}Tc does not replace electrocardiography and should not be the first test ordered in evaluating a patient with chest pain. However, in those patients for whom a diagnosis remains uncertain, pyrophosphate scintigraphy can be extremely useful. In attempting to rule out AMI, a negative study offers a 90 percent probability that this diagnosis can be excluded. However, a localized pattern of the highest intensity grade is virtually diagnostic of AMI, and a localized pattern alone is very strong but not absolute evidence for AMI.

KENNETH P. LYONS, MD
HAL OLSON, MD

REFERENCES

Poliner LR, Buja LM, Parkey RW, et al: Clinicopathologic findings in 52 patients studied by technetium-99m stannous pyrophosphate myocardial scintigraphy. Circulation 59:257-267, Feb 1979

Lyons KP, Olson H, Aronow W, et al: Sensitivity and improved specificity of a localized pattern of ^{99m}Tc pyrophosphate myocardial scintigraphy for the diagnosis of acute myocardial infarction. J Nucl Med 20:660, Jun 1979

Bonte FJ, Parkey RW, Graham KD, et al: A new method for radionuclide imaging of myocardial infarcts. Radiology 110:473-474, Feb 1974

ADVISORY PANEL TO THE SECTION ON NUCLEAR MEDICINE

WILLIAM H. BLAHD, MD
Advisory Panel Chairman
Section Editor
CMA Scientific Board Representative
Los Angeles

GILBERT GREENSPAN, MD
CMA Section Chairman
San Diego

LEONARD SWANSON, MD
CMA Section Secretary
Los Angeles

RICHARD MYERS, MD
CMA Section Assistant Secretary
Berkeley

NORMAN E. POE, MD
Loma Linda University

JOSEPH KRISS, MD
Stanford University

GERALD DENARDO, MD
University of California, Davis

KENNETH LYONS, MD
University of California, Irvine

DAVID KUHL, MD
University of California, Los Angeles

WILLIAM L. ASHBURN, MD
University of California, San Diego

ROBERT HATTNER, MD
University of California, San Francisco

JAN SIEMSEN, MD
University of Southern California
Los Angeles

WILLIAM T. MCLAUGHLIN, MD
Saratoga

NAOMI ALAZRAKI TAYLOR, MD
San Diego

EDITORIALS

Violence by Handguns

THE RECENT assassination attempt on President Reagan may well result in some form of legal control such as the registration or outlawing of handguns. But it is only naive to believe that the passage of any law will either do away with handguns or with their misuse. For the foreseeable future there will always be handguns around for those who wish to use them. Banning or registering them may help some but can in no way be expected to solve the problem.

The use of handguns for violent acts has always been more or less endemic in this country but in recent years seems to have become almost epidemic. Perhaps the problem should now be viewed as an epidemic. In an epidemic, efforts are made to immunize susceptible hosts or to control the agents of transmission, or both. In the instant case the disease may be described as the use of handguns for violent acts by susceptible hosts who somehow have become infected with the virus of this behavior. How then can such an epidemic be controlled?

It is suggested that efforts at control could be directed to the susceptible hosts, to the lethal instruments or to the agents of transmission of this method of violent behavior. We know of no way to immunize the susceptible hosts or even to identify them accurately, and it is unlikely that the lethal instruments themselves, the guns, can be adequately controlled. What then are the agents of transmission and can anything be done about them?

If one were to look detachedly at our television programs, motion pictures and news media one might easily conclude that this nation has considerable infatuation with violence by handguns, whether in the world of entertainment or in the events of the day. One might reasonably conclude that Americans not only condone violence by handguns but actually enjoy it. It seems almost too much to expect that this epidemic, which causes so much injury and so many deaths, can be brought under control as long as the agents of transmission are effectively reaching so many susceptible hosts with such acceptance and approval from the public at large.

—MSMW

Ascites

ASCITIC FLUIDS usually form slowly. This is a clinical problem in that ascites is often recognized only when garments become unexpectedly restrictive. If severe pain with peritoneal irritation is present, ascites is usually considered to reflect an acute or subacute abdominal condition. Ascites associated with either abnormalities of liver function or a history of heavy alcohol intake is too often labeled and treated as cirrhotic ascites without adequate investigation. Such premature evaluation and treatment may lead to overzealous use of loop diuretic agents or even the LeVeen peritoneal jugular shunt.

The specialty conference in this issue discusses an unusual problem of recurrent ascites and illustrates clearly the need to determine its cause in order to initiate specific therapy. Such an investigation must include microscopic examination of the ascitic fluid and the use of some sort of biochemical method, such as analysis of its protein levels, to separate fluids into transudates, where increased quantities of normal capillary fluid appear often from venous blockage, and exudates, in which an inflammatory component changes capillary permeability. The specialty conference provides an excellent review of some of the methods used to separate *transudates* from *exudates*. The

difficulty in the end, however, is not in the choice of biochemical test but in the correct interpretation of the variable features within a single disease entity that is causing ascites.

The acute onset of ascites associated with liver necrosis, as in severe drug hepatitis or unstable cirrhosis, may be associated with inflammation, resulting in exudative features that are in contrast to the customary transudation of the ascitic fluid. Both cancer and tuberculosis cause ascites by seeding the peritoneum with many nodules; however, they may also block lymphatics or the portal vein with nodules. In miliary seeding, the ascitic fluid is very high in protein and is clearly exudative, with malignant cells seen on cancer cytology or with tubercle bacilli demonstrated, respectively. In contrast, in portal vein obstruction the fluid may be a transudate free of specific agents. All intermediate gradations are seen.

Ascitic fluid with more than 3.0 to 3.5 grams per dl of protein or more than 300 cells per cu mm is almost always exudative. Applying complex ratios of serum to ascitic proteins or specific larger proteins to better discern capillary leaks increases specificity only moderately. Nearly all of these techniques have increasingly false-positive results when applied to all diagnostic problems involving ascites rather than when limited to well-characterized cases.

It seems clear that more errors are made because of failure to sample the ascitic fluid for diagnosis rather than failure to apply a newer test. All ascites of unknown origin requires study of the fluid, including measurement of protein content, cell count and differential. In most cases an amylase level, cytological examination for malignant cells and cultures for bacteria and mycobacteria should be obtained. When treatment is undertaken on the basis of a probable but not definite diagnosis, a follow-up examination should include a critical reevaluation of the patient's entire condition. If ascites persists, another fluid specimen should be obtained for further study.

When ascites is present, what value is there to be derived from its treatment? Prominent abdominal distention has an adverse cosmetic effect and its successful treatment often encourages the patient to comply with the total therapy. But what other impressive advantages accrue from treatment? A few benefits are dramatic; thus, prominent umbilical hernias with injured and near gangrenous skin improve promptly with control of ascites; other hernias require control of ascites before surgical repair can be maintained. Lower lobe pneumonia and stasis ulcers of the legs usually respond more rapidly when ascites is diminished. Portal pressure is lowered by control of ascites in patients who have had recent bleeding from varices and this is generally done. Other advantages often evoked in theory seldom materialize in reality. Patients with poor appetites rarely regain them and patients refractory to diuretic therapy seldom become responsive after paracentesis.

In most patients with ascites (other than in cases due to a malignant lesion), the condition improves and remains improved because of some substantive change in the cause of the ascites—a specific inflammatory cause subsides, a surgical correction is effected, alcoholic liver disease heals due to abstinence or portal pressure falls in response to treatment. Diminished dietary sodium and diuretic therapy (such as combinations of spironolactone and furosemide) usually control ascites for a time, but if the basic process worsens or the condition is absolutely stable, compliance drops off and in many patients ascitic fluid reaccumulates despite apparent continued treatment. This unsatisfactory long-term outcome in treatment of nonspecific ascites should mandate even more efforts to make a definitive initial diagnosis. Constrictive pericarditis, occlusion of the hepatic veins or suprahepatic vena cava, pancreatic ascites, tuberculous peritonitis, active liver disease (due to continued ingestion of drugs or alcohol) or steroid-responsive liver disease occur frequently among patients referred for refractory ascites.

The LeVeen peritoneal-jugular shunt relieves ascites in some patients by the reinfusion of ascitic fluid into the venous circulation. When critical criteria for its use are demanded, it is clear that well under 10 percent of the patients who have ascites are eligible for the procedure. The complications of this shunt are many, including sepsis, activated coagulation with disseminated intravascular coagulation and thrombosis of the shunt. These are sufficiently well known to lessen enthusiasm, and most of us are awaiting the outcome of the current randomized controlled trials before establishing our own patterns of use.

Ascites is an important sign of disease; its long-term control is possible only when the underlying condition is correctly diagnosed and, if possible, effectively treated. The cosmetic control of ascites without a careful diagnosis and follow-up is harmful to some patients because symptoms are allevi-

ated and the motivation for determining the underlying cause of ascites in order to provide appropriate therapy may be lessened.

FRANK L. IBER, MD
Professor of Medicine
Chief, Gastroenterology
University of Maryland Hospital and the Loch Raven Veterans Administration Medical Center
Baltimore

Financial Aid for Medical Students

EVENTS ARE CONSPIRING to intensify the financial problems of many needy medical students and of some who may not be so needy. The costs of going to medical school (often while raising a young family as well) have risen sharply, and the numbers of dollars available for student loans and other kinds of student aid are beginning to fall off, also sharply. Some schools and some students are more affected than others, but the overall problems are both immediate for many students and long-term for the profession. As might be expected, inflation and recent federal retrenchments are at the root of what for some is a true financial crisis. The recent and proposed federal retrenchments include an abrupt reduction in capitation funds for medical schools and a sharp curtailment of dollars and loan guarantees for medical student aid. No doubt this results partly from the current belief that there are now enough and maybe too many young doctors in the educational pipeline.

Some figures may be useful. Many physicians may be unaware that the tuition in a substantial number of medical schools is now up to $8,000 to $10,000 a year—with no guarantee for what it might become a year or two hence. As federal support drops off it is clear that more of the cost of medical education will have to be borne by students as tuition rises. Student indebtedness is growing. In 1971, for example, 72 percent of graduating seniors had an average indebtedness of $5,500. By 1979 there were 76 percent who had an average indebtedness of $15,800, with 30.7 percent being in debt for more than $20,000. The figures for 1981 are not yet available, but there are some senior medical students who will owe as much as $65,000 upon graduation. The money which must come from somewhere for medical student aid of all kinds amounts to several million dollars per medical school, and today's interest rates on commercial loans often place them well out of the reach of medical students.

The adverse effects of these financial problems of needy medical students are easily seen. Three seem particularly obvious. First, some will simply not be able to pay the tuition in addition to their other expenses and will have to drop out of school for a year or two, or even permanently, and this has begun to happen. Second, students who make it through medical school and start practice with high costs for such things as insurance, equipment and perhaps a young family, in addition to a heavy indebtedness, understandably may tend to place a high priority on an adequate income for themselves at the expense of any ideals of service which may have been among the reasons they chose a career in medicine in the first place. And, third, if it comes to pass that only the affluent can afford to go to medical school at all, this would be a giant step backward at a time when there is great progress toward having a population of physicians that reflects the ethnic, cultural and economic characteristics of the nation. There is much in all this that surely will not be healthy for medicine, for patients or for society as a whole.

What is to be done? The problem is not likely to go away in the foreseeable future. The issue for the medical profession is what the next generation of physicians will be like, and what will be their attitudes toward the traditional ethos of our profession. It would seem that for many these attitudes may be unduly colored by the financial circumstances under which they must begin their life of practice. If this is true then the financial burden of at least the more needy medical students should be lessened. Where can the money come from? Perhaps it is time that practicing physicians take a more direct interest in those who will be the future of our profession by individually and collectively sponsoring future physicians who need financial help to complete their training. It is surely important that medical students emerge from their training as good physicians dedicated to the highest traditions of professional service, and also that in the future no one be denied the opportunity to go to medical school simply because he or she does not happen to be sufficiently affluent.

Any medical school dean will be glad to hear from any physician or group of physicians interested in assisting needy medical students.

—MSMW

CASE REPORTS

Refer to: Boehme WM, Kurnick JE: Autoerythrocyte sensitization. West J Med 134:441-442, May 1981

Autoerythrocyte Sensitization

WILLIAM M. BOEHME, MD
Kalispell, Montana

JOHN E. KURNICK, MD
Irvine, California

THE SYNDROME OF autoerythrocyte sensitization (AES) was first described in 1955 by Gardner and Diamond.[1] The condition is characterized by the development of painful ecchymoses, either spontaneously or at sites of minimal trauma. Ecchymoses are frequently preceded by a prodrome of pain or itching at the site. Results of all clotting studies are normal. However, the patients have a sensitivity to their own red blood cells injected intradermally. At least one patient has also been found to be sensitive to phosphatidylserine, a constituent of red cell stroma.[2] Patients with AES are characteristically not sensitive to intradermal injections of hemoglobin, plasma, leukocytes or deoxyribonucleic acid (DNA), but some cases of sensitivity to hemoglobin and DNA have been recorded.[3] Numerous cases of AES have been reported in the 25 years since Gardner and Diamond first described the syndrome, and nearly all have occurred in women. Because psychophysiologic complaints have been such a frequent concomitant of AES,[4] the syndrome has also been referred to as psychogenic purpura.[5] We describe here a case of AES recently studied at the University of Colorado Medical Center.

Report of a Case

A 26-year-old white woman, a nurse, was referred to the University of Colorado Medical Center with a three-month history of bruising of the arms and legs. The bruises appeared spontaneously and were not associated with trauma. Lesions were frequently, but not invariably, preceded by an uncomfortable sensation of warmth in the area occurring 12 to 24 hours before the appearance of the lesion. There were no other bleeding manifestations, and the patient said that melena, hematuria and menorrhagia had not occurred.

Her past history was noteworthy in that three years previously surgical procedures had been done to relieve a thoracic outlet syndrome and the following year for bilateral carpal tunnel syndrome, both without abnormal bleeding. She had documented hypothyroidism of one year's duration corrected by thyroxine, and had been receiving tranquilizers at various times in the past for anxiety and depression. She had never been married, and said that she had few close friends of either sex. Her father had been a minister. He and two of the patient's sisters were killed in an avalanche in 1963 while driving to deliver an Easter sermon. An historical marker commemorates their deaths.

Physical examination was entirely unremarkable except for moderate obesity, an unconcerned affect and multiple 2- to 3-cm ecchymoses over both arms and legs with a few on the abdomen and back as well. The distribution of these ecchymoses equally on the medial and lateral aspects of all four extremities made it unlikely that they were self-inflicted. The hemoglobin reading was 13.4 grams per dl, leukocyte count 7,800 per cu mm with a normal differential, and platelet count 286,000 per cu mm. Extensive serum chemical analyses disclosed no abnormalities, and rheumatoid factor, antinuclear antibody and VDRL studies were all negative. Prothrombin time and partial thromboplastin time were normal at 12 seconds and 30 seconds, respectively. Ivy bleeding time, factor VIII assay and platelet aggregation studies were also within normal limits.

The patient was skin tested for AES as follows: Autologous whole blood, red blood cells, hemolyzed red cell stroma, hemoglobin, plasma and buffy coat cells were prepared as described by Gardner and Diamond.[1] Phosphatidylserine (ob-

From the Divisions of Hematology, University of Colorado Medical Center, Denver, and University of California, Irvine. Dr. Kurnick is now affiliated with the University of California, Irvine.

Submitted, revised, July 31, 1980.

Reprint requests to: William M. Boehme, MD, 210 Sunnyview Lane, Suite 204, Kalispell, MT 59901.

TABLE 1.—*Results (in Centimeters of Induration and Ecchymosis) After Intradermal Injection of 0.1 ml of the Substance Indicated*

	24 hours	*48 hours*
Autologous whole blood	1.1	1.5
Autologous red blood cells (hematocrit 75 percent)	2.2	3.0
Autologous hemolyzed red cell stroma	2.0	2.5
Autologous hemoglobin	2.5	2.0
Normal saline	0	0
Autologous plasma	0	0
Autologous buffy coat cells	0	0
Phosphatidylserine 200 μg	2.0	2.0
Phosphatidylserine 100 μg	1.6	3.0
Phosphatidylserine 25 μg	0.5	0.7

tained from Mann Research Laboratories) was serially diluted with sterile saline solution. As shown in Table 1, she reacted strongly to her own red cells, hemoglobin, hemolyzed red cell stroma and phosphatidylserine, but not to saline, plasma or buffy coat cells. With the exception of the positive reaction to autologous hemoglobin, these results are characteristic of AES. She returned two months later at which time she was not actively bruising. Repeat skin tests, however, showed a similar pattern. She has remained free of any evidence of massive bleeding, but has continued to have episodic ecchymoses on the extremities.

Discussion

AES has been described as occurring almost exclusively in females. Both immune and psychogenic phenomena have been implicated in its pathogenesis. Although not described as a clinical entity until 1955, AES is now believed to have played a role in the religious stigmata exhibited in the Middle Ages by women who reportedly bled from the hands and feet during the Easter season. This patient's history of having lost her minister father in an unusual accident is of interest in this regard. The positive skin test to autologous hemoglobin, although not characteristic, has been reported in a previous case.[3] The benign course followed by this patient is characteristic. Diamond reported a 13-year follow-up on two of the originally reported AES cases.[6] Although neither had lost her unusual sensitivity to autologous erythrocytes, both had improved considerably and were leading reasonably normal lives. Pregnancy in one and surgical operation in the other were tolerated without major complications.

REFERENCES

1. Gardner FH, Diamond LK: Autoerythrocyte sensitization: A form of purpura producing painful bruising following autosensitization to red blood cells in certan women. Blood 10:675-690, Jul 1955
2. Groch GS, Finch SC, Rogoway W, et al: Studies in the pathogenesis of autoerythrocyte sensitization syndrome. Blood 28:19-33, Jul 1966
3. Kremer WB, Mengel CE, Nowlin JB, et al: Recurrent ecchymoses and cutaneous hyperreactivity to hemoglobin: A form of autoerythrocyte sensitization. Blood 30:62-73, Jul 1967
4. McDuffie FC, McGuire FL: Clinical and psychological patterns in autoerythrocyte sensitivity. Ann Intern Med 64:255-265, Aug 1965
5. Ratnoff OD, Agle DP: Psychogenic purpura: A re-evaluation of the syndrome of autoerythrocyte sensitization. Medicine 47:475-500, Nov 1968
6. Diamond LK: Autoerythrocyte sensitization. JAMA 203:607, Feb 19, 1968

Refer to: Dart CH Jr, Braitman HE, Larlarb S: Gunshot penetrating injuries of the descending thoracic aorta. West J Med 134:442-446, May 1981

Gunshot Penetrating Injuries of the Descending Thoracic Aorta

CHARLES H. DART, Jr, MD
HOWARD E. BRAITMAN, MD
SOMBOON LARLARB, MD
Oxnard, California

HISTORICALLY, successful repairs of penetrating thoracic aortic injuries have been few.[1] Before 1970 most repaired wounds were stab inflicted. Surgical therapy was possible in many instances because of the small size of the wound, intrapericardial location of the lesion or temporary occlusion of the laceration by hematoma or thrombosis.[2] Military experience from the Vietnam conflict, the advent of acute trauma centers and advanced cardiovascular surgical techniques have produced higher incidence of successful surgical repair in thoracic penetrating wounds in the last decade. In civilian trauma practices 4 percent of arterial injuries involve the aorta, two thirds of these being the thoracic aorta.[1]

Descending thoracic aorta penetrating injuries

From St. John's Hospital, Oxnard, California, and the Department of Thoracic Surgery, UCLA School of Medicine, Los Angeles.

Submitted May 30, 1980.

Reprint requests to: Charles H. Dart, Jr, MD, 500 Esplanada Drive, Suite 700, Oxnard, CA 93030.

make up slightly more than 60 percent of all thoracic aortic injuries.[3] A diagnosis of penetrating wounds is suspected when the posterior mediastinal space has been transected and there is massive and continuous bleeding in the left pleural space or widening of the mediastinum. Diagnosis by arteriography in these cases is usually not possible because of cardiovascular instability. An emergency operation most commonly is done to confirm a suspected diagnosis, and this aggressive operative management has been instrumental in improving the incidence of successful repair.[3]

Three cases are presented of gunshot wounds of the descending thoracic aorta in patients seen between June 1978 and July 1979. The diagnostic findings and management are discussed.

Reports of Cases

CASE 1. A 28-year-old man was admitted to hospital with a wound of the upper abdominal area caused by a handgun. On arrival to the emergency room he was in hypovolemic shock. His condition was stabilized with colloid and electrolyte solutions. An x-ray study of the chest showed a missile in the left lower thorax with moderate hemothorax and a wide mediastinum. Abdominal films showed the presence of air and fluid. On immediate abdominal exploration a through-and-through stomach wound and diaphragmatic penetration anterior to the aortic hiatus were noted. The abdominal incision was extended through the costal margin in the seventh intercostal space and the diaphragm was split in a thoracoabdominal extension. There was a large mediastinal hematoma with an anterior penetrating aortic missile wound and a ragged 1.5-cm posterior laceration of the aortic wall. Periaortic and adventitial tissues assisted in containing the hemorrhage. The blood pressure during the induction was low at 50 to 60 mm of mercury. Following aortic cross-clamping above and below the lesion there was some improvement. No heparin was given. Repair was carried out using a woven tube Dacron graft and 3-0 Prolene suture. Aortic cross-clamp time was 24 minutes. The patient's postoperative course was uneventful, and a thoracic arteriogram obtained six weeks postoperatively indicated good patency.

CASE 2. A 31-year-old man sustained a wound from a large-caliber handgun of the left lateral portion of the chest. He arrived at the emergency department in shock with a large left-sided hemothorax, shown on an x-ray study of the chest (Figure 1). After resuscitation the patient was taken immediately to the operating room where an exploratory thoracotomy through the fifth interspace was done. The blood pressure was 50 to 60 mm of mercury during induction and initial phase of the operation. A large mediastinal hematoma was found to be actively bleeding into the left side of the chest, which contained several units of blood. The aorta was immediately controlled at the level of the hilum of the lung and at the diaphragm. There was a ragged wound on the lateral aspect of the aorta, approximately 2 cm long and about a third the circumference of the descending thoracic aorta. Repair was carried out with a Dacron woven patch and 3-0 Prolene suture. Cross-clamp time was ten minutes. Asso-

Figure 1.—(Case 2) Preoperative x-ray study of the chest.

ciated lesions were bleeding in the upper and lower lobes of the lung and also through a lacerated intercostal artery at the seventh rib, the entrance site of the bullet. A Haemonetics Cell Saver Autogenous Recovery System (Haemonetics Corporation, Braintree, MA) was used to retransfuse 6 to 8 liters of blood. The postoperative course was unremarkable. An x-ray study of the chest (Figure 2) and an arteriogram (Figure 3) illustrate the postoperative condition of the wound.

CASE 3. A 21-year-old man entered the hospital with a gunshot wound to the epigastric area. The patient was in shock in the emergency department and resuscitation was attempted with type-specific blood and colloid and crystalloid solutions. The blood pressure, initially unobtainable, was measured at 70 to 80 mm of mercury (systolic) following these attempts. An x-ray study of the chest showed a left-sided hemothorax. Free air and a large stomach filled with blood were seen on abdominal films. Nasogastric drainage was grossly bloody.

The patient was taken immediately to the operating room and his condition explored through a midline upper abdominal incision. Grossly bloody fluid was obtained from the abdominal cavity, bullet wounds were found through and through the left lobe of the liver and in the lesser stomach curvature. A large retroperitoneal hematoma was also found and a large volume of gastric blood clot and fluid. A diaphragmatic bullet wound anterior to the aortic hiatus was observed. The blood pressure was unobtainable at this time. The abdominal incision was converted quickly to a thoracoabdominal incision through the diaphragm in the seventh intercostal space. Proximal aortic cross-clamping to the descending aorta was accomplished. Dissection above the diaphragm in the posterior mediastinum showed a through-and-through esophageal bullet wound communicating with a hematoma about a ragged 1.5 by 2.0 cm lateral aortic laceration. A patch graft of woven Dacron was sutured into the defect using 3-0 Prolene. Aortic cross-clamping time was 26 minutes. Rapid closure of his gastric and esophageal wounds was accomplished. Despite transfusion the blood pressure remained low.

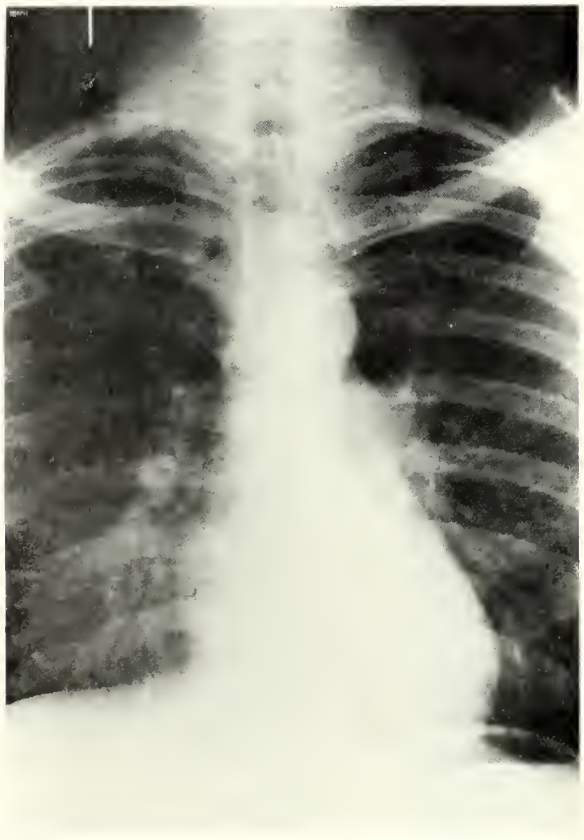


Figure 2.—(Case 2) Postoperative x-ray study of the chest.

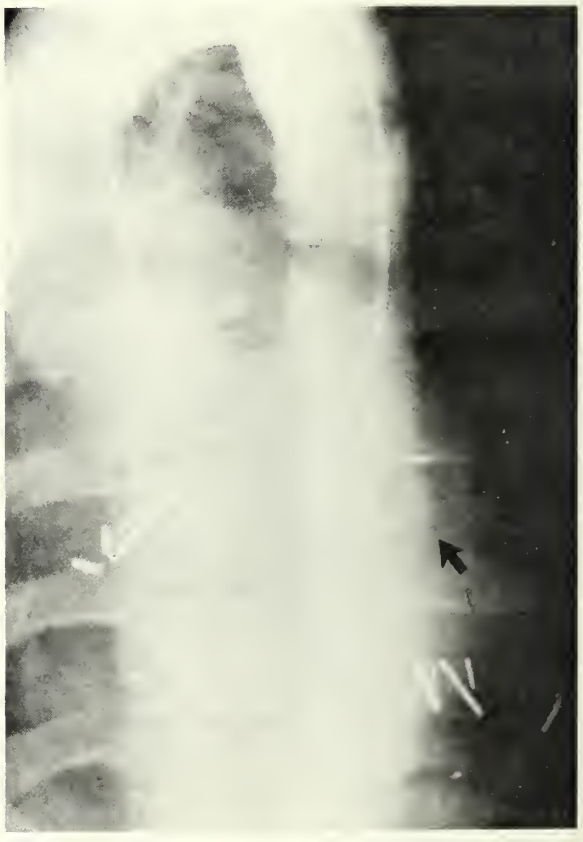


Figure 3.—Postoperative thoracic arteriogram showing site of patch graft repair (arrow).

After copious irrigation, Haemonetics Cell Saver Autotransfusion (Haemonetics Corporation, Braintree, MA) was used because of the unavailability of type-specific blood.

Following closure of the wounds, the patient's postoperative condition remained poor with continued oozing through drain sites and deteriorating respiratory function. The patient died on the first postoperative day.

Results

All patients were in shock on arrival to the emergency department. No preoperative arteriography was possible because of massive blood loss. One patient had a standard left-sided thoracotomy and two had midline abdominal incisions converted to seventh interspace thoracoabdominal extensions. All patients had prosthetic woven Dacron graft repairs, one a tube and the other two, patch grafts. Temporary aortic occlusion was used in all cases, and no neurological or ischemic impairment was attributed to this occlusive period. Associated injuries involved the lung, liver, stomach, esophagus and intercostal artery. All patients survived the immediate operative procedure, one patient died early postoperatively from disseminating intravascular coagulation and respiratory failure. Postoperative arteriograms were obtained in the two long-term survivors. Autotransfusion with Haemonetics Cell Saver was used in two instances because of the large volume of blood lost and the scarcity of replacement blood.

Discussion

Resuscitation management of penetrating thoracic aortic injuries involves large volume replacement of colloid and crystalloid solutions as well as of blood. Early surgical intervention may be the only diagnostic procedure. Aortography, frequently necessary in blunt aortic lacerations,[4] is not always possible because of the patient's unstable hemodynamic state. Rapid operative control of the hemorrhage site is the most singularly effective resuscitation maneuver. Autotransfusion has been helpful when blood supplies were scarce. Unfortunately, retransfusion is possible only if gastrointestinal secretions and content are contained. Retransfusion also has not replenished clotting factors shed during hemorrhage.

Associated injuries with aortic penetrating wounds have not been found to be as significant a factor as with blunt aortic lacerations[4]; the addition of serious injuries to massive bleeding from penetrating aortic wounds has not been well tolerated. Lung contusion has contributed to postoperative respiratory ventilation problems in some instances.

Management of the descending thoracic aortic injury site can be handled by direct suture. Due to the tissue destruction about the injury site, however, prosthetic graft material was used in the presented cases. When the site is contaminated by gastrointestinal content, serious consideration should be given to using a sleeve or a patch constructed of reverse saphenous vein. Urgency of repair may preclude this as in the presented cases. Simple aortic cross-clamping as advocated by Crawford and co-workers,[5] can be tolerated for up to 30 minutes without ischemic sequelae. The use of a TDMAC (tridodecylmethyl ammonium chloride) shunt suggested by Gott and colleagues[6] has been considered but was not used because of the relative hypotension in the presented cases. The hypotension would have limited flow through the shunt and into the distal body perfusion bed.

Postoperative arteriography was carried out in the survivors to provide baseline studies. The use of woven graft and monofilament suture material would seem to make this desirable.

Summary

Penetrating injuries of thoracic aorta, although not particularly common, are lethal. When tissue destruction is small, as in a stab wound, prognosis is related to early diagnosis and operative repair. Gunshot wounds, usually involving much greater velocity and destruction, present far more serious problems in their management.

Three cases of gunshot wounds of descending thoracic aorta were examined and treated. All had visceral injuries of varying degrees including stomach, liver and lung. In all three patients prosthetic graft replacement was required. Two patients, long-term survivors, had postoperative aortography for baseline evaluation of vascular repair.

Management of gunshot wounds of descending thoracic aorta centers around massive and continuous blood loss which makes resuscitation and diagnostic arteriography difficult and requires early operative intervention. Associated injuries to liver, stomach and lungs may increase difficulties with resuscitation, chances of infection and pulmonary complications. The destruction path associated with gunshot wounds causes significant

damage to the vessel wall, necessitating temporary aortic occlusion and prosthetic graft repair.

REFERENCES

1. Rich NM, Spenser FC: Vascular Trauma. Philadelphia, WB Saunders, 1978, pp 427-428
2. Symbas PN, Sehdeva JS: Penetrating wounds of thoracic aorta. Ann Surg 171:441, 1970
3. Reul J, Beall AC, Jordan GL, et al: The early operative management of injuries of the great vessels. Surg 74:862-873, 1973
4. Dart CH, Braitman HE: Traumatic rupture of thoracic aorta. Arch Surg 111:697-702, 1976
5. Crawford ES, Fenstermacher JM, Richardson W, et al: Reappraisal of adjunct to avoid ischemia in treatment of thoracic aortic aneurysms. Surgery 67:182, 1970
6. Demeester TR, Cameron JL, Gott VL: Repair of a through and through gunshot wound of the aortic arch using a heparinized shunt. Ann Thorac Surg 16:193-198, 1973

Refer to: Chudwin DS, Cowan MJ, Wara DW, et al: Lung involvement in progressive vaccinia. West J Med 134:446-448, May 1981

Lung Involvement in Progressive Vaccinia

DAVID S. CHUDWIN, MD
MORTON J. COWAN, MD
DIANE W. WARA, MD
ALAN C. JOHNSON, MD
San Francisco

PROGRESSIVE VACCINIA is an uncommon but serious complication of smallpox vaccination characterized by continuing enlargement and often necrosis of the vaccination site, sometimes with satellite or metastatic lesions.[1-3] It usually occurs following smallpox vaccination of patients with immunodeficiency disorders, either primary or secondary to malignancy or cytotoxic drugs.[2-4] Pulmonary involvement with progressive vaccinia has been suggested,[3-5] but antemortem culture of virus from the lungs has not been reported. We present the case of a 7-month-old boy with previously undiagnosed combined immunodeficiency in whom fatal progressive vaccinia developed after smallpox vaccination. Vaccinia virus was cultured and identified from an antemortem needle aspiration of the lung. This case reemphasizes that effective cellular immunity is required for recovery from progressive vaccinia and that smallpox vaccination can result in fatal complications.

ABBREVIATIONS USED IN TEXT

PHA = phytohemagglutinin
VIG = vaccinia immune globulin

Report of a Case

The patient was a 7-month-old Oriental boy who was well until 3 months of age when recurrent stomatitis developed. At 5½ months he received a smallpox vaccination to treat the stomatitis, which was attributed to herpes simplex. The lesion, over the left deltoid, failed to scab and the first satellite lesion appeared approximately ten days after vaccination.

On admission to Moffitt Hospital, University of California, San Francisco, 30 days after vaccination, he had a temperature of 38°C (100.4°F) and a 3 by 4.5 cm shallow nonnecrotic ulcer with a vesicular border on his left arm. A satellite lesion 0.75 cm in diameter was nearby, and a 2-cm lesion was present on the right thigh where the infant had scratched himself. There was no erythema around any of the lesions. No lymph nodes were palpable and no tonsillar tissue was seen. His respiratory rate was 64 breaths per minute; scattered rhonchi, but no rales, were heard on chest examination. Hepatosplenomegaly was not present initially.

Immunologic studies gave the following results: total lymphocyte count 1,314 per cu mm, absent T-cell rosettes; absent lymphocyte response to phytohemagglutinin (PHA) and to allogeneic cells; IgG 100 mg per dl (normal 427 ± 186), IgM 60 mg per dl (normal 43 ± 17), and no detectable IgA (normal 28 ± 18). Red cell adenosine deaminase and nucleoside phosphorylase levels were normal.

Vaccinia virus was cultured from a swab of the left arm lesion by inoculation of human fetal diploid kidney and primary monkey kidney cells in culture. No neutralizing antibodies to vaccinia were detected in the patient's serum. The vaccinia infection was treated with gamma globulin, fresh frozen plasma, five injections (total 35 ml) of vaccinia immune globulin (VIG), five 3-day courses of methisazone (200 mg per kg of body weight loading dose, then 50 mg per kg every six hours),

From the Department of Pediatrics, University of California, San Francisco.

Submitted, revised, June 5, 1980.

Supported in part by the Pediatric Clinical Research Center (PCRC) Grant NIH 5M01, RR00-79-16.

Reprint requests to: David S. Chudwin, MD, Department of Pediatrics, 679M, University of California, San Francisco, San Francisco, CA 94143.

one unit of transfer factor from a person recently vaccinated against smallpox, and topical therapy to lesions including adenine arabinoside, rifampin and gentian violet. No HLA-compatible bone marrow donor was found, so a 12½ week gestational age fetal thymus was injected intraperitoneally on the 29th hospital day. Follow-up studies 6 and 15 days after the fetal thymus transplant showed no new HLA antigens, no increase in T-cell rosettes, and only a minimal increase in PHA response (754 counts per minute stimulated/122 cpms resting) at 15 days posttransplant. Despite treatment, new lesions developed on the trunk, face and extremities, and hepatosplenomegaly was noted.

An x-ray study of the chest done shortly after admission showed a patchy bilateral infiltrate (Figure 1). The patient became increasingly tachypneic and needle aspiration of his right lung on the 9th hospital day showed *Pneumocystis carinii* to be present; cultures were negative for vaccinia and other viruses. His respiratory status improved with treatment for ten days with pentamidine isethionate and trimethoprim sulfamethoxazole. Blood, urine, stool and cerebral spinal fluid cultures were negative for viruses. However, vaccinia virus was cultured from a nasopharyngeal swab obtained on the 34th day. Acute respiratory failure developed on the 38th day with tachypnea, wheezing and cyanosis, which required endotracheal intubation and mechanical ventilation. An x-ray film of the chest showed a small amount of fluid in the right upper lobe and a bilateral interstitial infiltrate. A second lung aspiration on the 41st hospital day was negative for *Pneumocystis* organisms; however, no sample was sent for viral isolation. The patient's respiratory status deteriorated. On the 49th hospital day, a third needle aspiration was carried out. Vaccinia virus was cultured and identified from sterile saline injected and then withdrawn from the right lung. No bacterial organisms grew and again *Pneumocystis* organisms were not seen. An x-ray film of the patient's chest at that time showed a fluid-filled right upper lobe and a bilateral patchy interstitial infiltrate (Figure 2). The patient died two days later in respiratory failure after an episode of cardiac asystole. Permission for an autopsy was denied.

Discussion

Both cellular and humoral immunity play a role in protection against vaccinia virus.[1,2,6,7] In infants and children, progressive vaccinia has been described in association with hypogammaglobulinemia and other B-cell disorders, with T-cell disorders, and with combined immunodeficiency.[2-6,8-12] In reports of five patients with combined immunodeficiency and progressive vaccinia,

Figure 1.—X-ray film of the chest made shortly after admission shows bilateral patchy infiltrates. *Pneumocystis carinii* was found on needle aspiration.

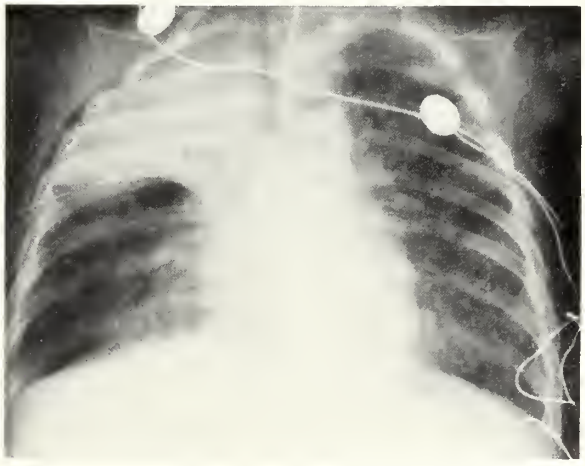


Figure 2.—X-ray study done before third needle aspiration shows bilateral patchy infiltrates, right pleural effusion and a consolidated right upper lobe. Vaccinia virus was cultured from the right lung.

all died. In three of the five there was evidence of lung involvement noted at autopsy.[3,5,8] In two of these patients pathologic lung changes were found that were consistent with vaccinia infection, and in the third the virus was isolated from the lungs and other organs at autopsy.[3,5] In two patients with thymic hypoplasia and abnormal immunoglobulin synthesis (Nezelof syndrome) and progressive vaccinia, no evidence for vaccinia involvement of the lungs was found at autopsy.[3] In most reports, patients with hypogammaglobulinemia and progressive vaccinia have survived; however, in two fatal cases in which autopsies were done, no lung involvement was noted.[3,6,9-12] Culture of vaccinia virus from the lungs of living patients has not been reported.

Our patient had severe combined immunodeficiency as shown by low immunoglobulin levels, absent response to PHA and allogeneic cells, and absent T-cell rosettes. We administered passive antibody to the patient with VIG, plasma, and gamma globulin, but were unsuccessful in reconstituting his cellular immunity by a fetal thymus transplant and transfer factor. Despite treatment, his lesions enlarged and he eventually died. This case confirms previous observations that, in addition to antibody, adequate cellular immunity is necessary for recovery from progressive vaccinia.[3]

No viruses were isolated from an initial lung aspirate in our patient. Subsequently, respiratory failure developed and endotracheal intubation was required. Two further lung aspirations showed no evidence for bacterial pathogens or recurrent *Pneumocystis carinii,* but vaccinia virus was cultured from the third lung aspirate. While it is possible that the virus was a skin contaminant, the needle insertion site was distant from any lesions, careful technique was used and no vaccinia was cultured from the first lung aspirate. The virus may have been introduced into the lungs from the upper respiratory tract through local spread or the endotracheal tube. Alternatively, systemic vaccinia may have led to pulmonary involvement. The positive nasopharyngeal culture before the onset of respiratory failure suggests the former, while the development of skin lesions at multiple noncontiguous sites, hepatosplenomegaly and the eventual fatal outcome argues for the latter hypothesis. Unfortunately, no autopsy could be done to confirm the pulmonary and possible systemic involvement.

This case is a further reminder that smallpox vaccination can result in fatal complications. There is now no medical indication whatsoever for smallpox vaccination in the United States.[13] Smallpox vaccination is ineffective in the treatment of herpetic infection.[2,14] Furthermore, smallpox vaccination is specifically contraindicated in children under one year old, in patients with inherited or acquired immunodeficiencies including those receiving chemotherapy, in patients with eczema or skin diseases, and in pregnant women.[1]

REFERENCES

1. Goldstein JA, Neff JM, Lane JM, et al: Smallpox vaccination reactions, prophylaxis, and therapy of complications. Pediatrics 55:342-346, 1975

2. Lane JM, Ruben FL, Abrutyn E, et al: Deaths attributable to smallpox vaccination, 1959 to 1966, and 1968. JAMA 212:441-444, 1970

3. Fulginiti VA, Kempe CH, Hathaway WE, et al: Progressive vaccinia in immunologically deficient individuals. Birth Defects Original Article Series 4:129-145, 1968

4. Lane JM, Ruben FL, Neff JM, et al: Complications of smallpox vaccination, 1968. N Engl J Med 281:1201-1207, 1969

5. Robinson MJ, Muragasu R, Thong YH, et al: A fatal case of progressive vaccinia—Clinical and pathological studies. Aust Pediatr J 13:125-130, 1977

6. Kempe CH: Studies on smallpox and complications of smallpox vaccination. Pediatrics 26:176-189, 1960

7. Freed ER, Duma RJ, Escobar MR: Vaccinia necrosum and its relationship to impaired immunologic responsiveness. Am J Med 52:411, 1972

8. Timar L, Budai J, Nyerges G, et al: Progressive vaccinia: Immunological aspects and transfer factor therapy. Infection 6: 149-153, 1978

9. Connolly JH, Dick GWA, Field CMB: A fatal case of progressive vaccinia. Br Med J 1:1315-1317, 1962

10. Jarkowski TL, Mohagheghi HA, Nolting WS: Vaccinia gangrenosa: Report of a case with hypogammaglobulinemia. Clin Pediatr 2:332-339, 1963

11. White CM: Vaccinia gangrenosa due to hypogammaglobulinemia. Lancet 1:969-971, 1963

12. Hansson O, Johansson SGO, Vahlquist B: Vaccinia gangrenosa with normal humoral antibodies. Acta Pediatr Scand 55: 264-272, 1966

13. Adverse reactions to smallpox vaccination—1978. Morbidity Mortality Weekly Rep 28:265-267, 1979

14. Kern AB, Schiff BL: Smallpox vaccinations in the management of recurrent herpes simplex: A controlled evaluation. J Invest Dermatol 33:99-102, 1959

Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

More HAFE

TO THE EDITOR: Drs. Auerbach and Miller are to be commended on their skilled and careful observations of the syndrome HAFE (high altitude flatus expulsion) reported in the February issue.[1] However, I would like to propose another etiologic mechanism.

I, too, have observed this phenomenon at similar altitudes and noted a predilection for its occurrence during the night and upon awakening in the morning, accompanied by borborygmus. It is known that arterial oxygen saturation drops to 88 percent in normal persons sleeping at 10,000 feet.[2] Acute decreases in arterial oxygen saturation at altitude may in turn lead to intestinal hypermobility and possible abnormalities of normal enzymatic and digestive function. Hyperactive bowels combined with other factors such as freeze-dried foods (high fiber content) and decreased barometric pressure (less than 500 mm of mercury at 11,000 feet) may provide a more fruitful explanation for this distressing syndrome.

EDWARD GEEHR, MD
Research Fellow
Department of Emergency Medicine
UCLA Hospital and Clinics
Los Angeles

REFERENCES

1. Auerbach P, Miller YE: High altitude flatus expulsion (HAFE) (Correspondence). West J Med 134:173-174, Feb 1981
2. Kryger M, Glas R, Jackson D, et al: Impaired oxygenation during sleep in excessive polycythemia of high altitudes: Improvement with respiratory stimulation. Sleep 1:3-17, Sep 1978

Gastrointestinal Barotrauma

TO THE EDITOR: In their exposé of the high altitude flatus expulsion (HAFE) syndrome, Auerbach and Miller[1] compared this entity to the development of decompression sickness in deep-sea divers. Actually, though, it would have been more appropriate to compare HAFE with the gastrointestinal barotrauma that occasionally occurs in divers because HAFE has exactly the same pathophysiology as this type of barotrauma.

Gastrointestinal barotrauma—which is also known as bowel barotrauma, aerogastralgia and gas in the gut—is caused by expansion of intraluminal bowel gas as ambient atmospheric pressure is decreased during ascent from a dive. It is manifested by eructation, flatus expulsion, abdominal fullness and colicky pain. Although it is rarely severe, it has been known to cause syncopal and shock-like states.[2]

Bowel barotrauma is seen more often in scuba divers than in deep-sea divers, who typically wear a full facemask or helmet, because scuba divers, especially if inexperienced, are more prone to swallowing air. Performing the Valsalva maneuver to clear the ears while in the head-down position during descent also forces air into the stomach. Other predisposing factors include drinking carbonated beverages or eating a heavy meal, particularly one containing legumes or other flatogenic substances, soon before diving, or chewing gum during the dive.

The only treatment that is usually needed for bowel barotrauma is slowing the rate of ascent or stopping ascent entirely until the excess bowel gas is vented. Sometimes, descent to a higher pressure is needed. Recompression is needed in only the most extreme cases.

Along this latter line, it is also relevant to note that hyperbaric oxygen therapy (HBOT) has been successfully used to treat some similar problems based on the converse principle that entrapped gas will decrease in size when compressed to elevated atmospheric pressure. Loder reported using HBOT to treat 12 cases of paralytic ileus which had failed conventional management.[3] Similarly, Kulak and co-workers reported using hyperbaric therapy to reduce the size of several intestinal catheter balloons and, thus, allow their removal when other methods of deflation had failed.[4] Also, HBOT has been used to treat pneumatosis cystoides intestinalis.[5]

Although HAFE and gastrointestinal barotrauma are of unlikely concern to most clinicians, it is of practical worth to remember that HBOT may be

potentially useful in treating various trapped gas syndromes that do not respond to conventional methods.

KENNETH W. KIZER, MD, MPH
Consultant in Diving and Hyperbaric Medicine
University of California, San Francisco Medical Center
San Francisco
President-Elect
North Pacific Chapter, Undersea Medical Society, Inc.

REFERENCES

1. Auerbach P, Miller YE: High altitude flatus expulsion (HAFE). West J Med 134:173-174, 1981

2. Edmonds C, Lowry C, Pennefather J: Diving and Subaquatic Medicine. Mosman, N.S.W., Australia, Diving Medical Centre, 1976, p 93

3. Loder RE: Use of hyperbaric oxygen in paralytic ileus. Br Med J 1:1448-1449, 1977

4. Kulak RG, Friedman B, Gelernt IM, et al: The entrapped intestinal balloon: Deflation by hyperbaric therapy. Ann Surg 187:309-312, 1978

5. Masterson JST, Fratkin LB, Osler TR, et al: Treatment of pneumatosis cystoides intestinalis with hyperbaric oxygen. Ann Surg 187:245-247, 1978

Alkalinization Therapy for Tricyclic Antidepressant Overdose

To the Editor: I appreciated the insight into treatment of cardiac arrhythmias caused by tricyclic antidepressant overdose provided by Hoffman and McElroy in their recent article.[1] However, I take issue with the recommendation that "alkalinization therapy" be used to treat quinidine overdose. One of the authors' own references[2] actually states that quinidine urinary excretion is inversely related to urine pH, and that QT lengthening, a quinidine-induced effect, increases as urine pH increases. This suggests that urine pH exerts a clinically significant effect.

Two other references cited by Hoffman and McElroy[3,4] mention administration of alkalinizing drugs during quinidine toxicity, but only in combating the patients' preexisting metabolic acidosis. In neither case was *alkalinization* considered the major thrust of treatment, and both articles mention that although this procedure has been advocated, it has not always proved beneficial.

A case which illustrates the potential danger of an alkaline urine pH concomitant with quinidine administration was reported by Zinn in 1970.[5] In a patient whose condition was stabilized with constant doses of quinidine and digoxin, electrocardiographic signs of quinidine toxicity began to occur. A quinidine level subsequently obtained was 25 μg per ml. When questioned, the patient was found to have begun recently making his urine alkaline with his diet and antacid tablets. Upon return to a normal diet, quinidine serum levels returned to the therapeutic range at his previous dose.

The administration of sodium bicarbonate may be necessary in treating quinidine toxicity if metabolic acidosis has occurred. In this case it would be used in conjunction with specific measures to combat quinidine's ill effects (hypotension, convulsions, arrhythmia). Sodium bicarbonate should not be advocated as one of these specific measures.

MARY LINDA H. STOTTER, PharmD
Methodist Hospital of Indiana
Indianapolis

REFERENCES

1. Hoffman JR, McElroy CR: Bicarbonate therapy for dysrhythmia and hypothermia in tricyclic antidepressant overdose. West J Med 134:60-64, Jan 1981

2. Gerhardt RE, Knouss RF, Thyrum PT, et al: Quinidine excretion in aciduria and alkaluria. Ann Intern Med 71:927-933, Nov 1969

3. Shub C, Gau GT, Sidell PM, et al: The management of acute quinidine intoxication. Chest 73:173-178, Feb 1978

4. Kerr F, Kenoyer G, Bilitch M: Quinidine overdose—Neurological and cardiovascular toxicity in a normal person. Br Heart J 33:629-631, Jul 1971

5. Zinn MB: Quinidine intoxication from alkali ingestion. Tex Med 66:64-66, Dec 1970

* * *

To the Editor: I read with interest Hoffman and McElroy's excellent article on bicarbonate therapy in tricyclic antidepressant overdose in the January 1981 issue.[1] I was glad that they have thereby focused attention on this somewhat neglected and quite effective treatment. It thus pains me to nitpick an excellent presentation, but their discussion of phenytoin deserves some amplification.

First, an error apparently occurred in preparation of the manuscript, and the reference cited[2] regarding the ineffectiveness of phenytoin (diphenylhydantoin) contains no mention of that drug whatsoever. There is, in fact, scant literature on this topic. Until recently, there was only one published report recommending phenytoin in humans, and this did not mention the number of cases or the results. The authors suggested a dose of either 200 mg given intramuscularly or 5 to 10 mg per kg of body weight intravenously as a useful prophylactic agent against "cardiac or cerebral arrhythmias."[3] Also until recently, the only other published data involved three dogs given amitryptyline until arrhythmias developed. Intravenously given phenytoin in varying doses had a brief antiarrhythmic effect at that time, but sinus rhythm was not restored.[4] At the same time, pulse and blood pressure fell significantly and respirations were depressed, even in the one animal receiving only 2 mg per kg of body weight. The two animals that received 15 to 17 mg of phenytoin per kg of body weight died several hours later.

Fortunately, the most detailed report yet made

has just been published.[5] This study of ten humans, all with QRS prolongation of 100 to 160 msec, clearly documented a mean decrease in QRS prolongation of 24 msec over a mean time of 39 minutes after intravenous loading with 5 to 7 mg phenytoin per kg of body weight. Other drugs were withheld, and acid balance and fluid volume were maintained at normal values. Although potential effects on preexisting hypotension were not evaluated, the conduction abnormalities were clearly reversed, and no further arrhythmias occurred in any of these patients. Thus, phenytoin seems a useful drug that warrants further investigation, although bicarbonate therapy or hyperventilation to a pH of 7.5 remains the most benign and thoroughly evaluated treatment.

MICHAEL CALLAHAM, MD
Associate Chief, Emergency Medicine
Highland General Hospital
Oakland, California

REFERENCES

1. Hoffman JR, McElroy CR: Bicarbonate therapy for dysrhythmia and hypotension in tricyclic antidepressant overdose. West J Med 134:60-64, Jan 1981

2. Slovis TL, Ott JE, Titelbaum DT, et al: Physostigmine therapy of acute tricyclic antidepressant poisoning. Clin Toxicol 4:451-459, Sep 1971

3. Davis JM: Overdose of psychotropic drugs. Psych Ann 3: 6-11, May 1973

4. Brown TCK: Tricyclic antidepressant overdosage: Experimental studies on the management of circulatory complications. Clin Toxicol 9:255-272, 1976

5. Hagerman GA, Hanashiro PK: Reversal of tricyclic antidepressant-induced cardiac conduction abnormalities by phenytoin. Ann Emerg Med 10:82-86, Feb 1981

* * *

Drs. Hoffman and McElroy Respond

TO THE EDITOR: We were pleased to review these two thoughtful letters regarding topics covered somewhat peripherally in our paper on alkalinization therapy for tricyclic antidepressant overdose. While neither addresses the major thrust of our article, both raise issues that are of significant interest.

Dr. Stotter is concerned about the use of alkalinization in patients with quinidine overdose. She correctly makes the point that this drug's urinary excretion is inversely related to urine pH,[1] which would tend to suggest that the use of sodium bicarbonate might in fact be harmful in such patients. We feel that there may be, nevertheless, overriding arguments in favor of bicarbonate in this situation. Serum quinidine levels are poor indicators of level of toxicity,[2] as the large majority of the drug is bound to protein and lipid moieties of the cell membrane.[3] It is thus not clear that the rate of excretion is a critical factor in this drug's toxicity. Furthermore, increasing serum pH increases protein binding of quinidine,[4] so that free drug levels do in fact decrease with alkalinization. Perhaps most important, hypokalemic effects of alkalinization may be critical in controlling the cardiotoxic effect of quinidine overdosage.[2,5] Unfortunately, empirical data on this subject are minimal. Nevertheless, there is reason to believe it may have significantly positive effects, and we believe it deserves further study.

We were somewhat surprised to read Dr. Callaham's objection to our brief discussion of the use of phenytoin in tricyclic antidepressant overdose. Let us first note that Dr. Callaham was in fact correct in assuming that there was a manuscript error with regard to our referencing. The appropriate reference was to number 33, an article by Bismuth and co-workers,[6] rather than 32, as mistakenly given. The Bismuth article, and several others,[7-10] referred to in Dr. Callaham's own excellent review of this subject, suggests a very limited role for phenytoin. Dr. Callaham concluded his own discussion of phenytoin (published in October 1979) as follows: "No well-described case documenting its effectiveness has been published, and it is illogical to advocate its use under these circumstances."

The recent article by Hagerman and Hanashiro,[12] to which Dr. Callaham refers in his letter, is indeed intriguing. The uniformly successful response to phenytoin in ten patients with prolonged QRS complexes or PR intervals (or both) should encourage further investigation. However, no blood levels were reported, none of the patients were acidotic, nor was there any other suggestion in the report that any of them was hypotensive. Likewise, the only dysrhythmia apparently seen in any of these patients was sinus tachycardia.

The role of phenytoin in the treatment of severe tricyclic antidepressant overdose remains unclear. Our own anecdotal experience has not been encouraging, and we see no reason, at this time, to alter our suggestion that alkalinization, combined with appropriate fluid management, is the treatment of first choice for hypotension and dysrhythmia secondary to tricyclic antidepressant overdose.

JEROME R. HOFFMAN, MD
Assistant Professor of Medicine
UCLA Emergency Medicine Center
CHARLES R. McELROY, MD
Associate Professor of Medicine
Director, UCLA Emergency Medicine Center
Los Angeles

REFERENCES

1. Gerhardt RE, Knouss RF, Thyrum PT, et al: Quinidine excretion in aciduria and alkaluria. Ann Intern Med 71:927-933, Nov 1969

2. Kerr F, Kenoyer G, Bilitch M: Quinidine overdose—Neurological and cardiovascular toxicity in a normal person. Br Heart J 33:629-631, Jul 1971

3. Luchi RJ, Helwig J, Conn HL: Quinidine toxicity and its treatment. Am Heart J 65:340, 1963

4. Conn HL, Luchi RJ: Some quantitative aspects of the binding of quinidine and related quinoline compounds by human serum alhumin. J Clin Invest 40:509, 1961

5. Shub C, Gau GT, Sidell PM, et al: The management of acute quinidine intoxication. Chest 73:173, 1978

6. Bismuth C, Pebay-Peyroula F, Frejaville J: Traitement acteul des cardiopathies toxiques. Concours Med 91 (Suppl) 21:4453-4470, 1969

7. Brown T: Tricyclic antidepressant overdosage: Experimental studies on the management of circulatory complications. Clin Toxicol 9:255-272, 1976

8. Biggs JT: Clinical pharmacology and toxicology of antidepressants. Hosp Pract, Feb 1973, pp 79-84

9. Burckhardt D, Raeder E, Muller V, et al: Cardiovascular effects of tricyclic and tetracyclic antidepressants. JAMA 239: 213-216, 1978

10. Coté M, Elias G: Le propranolol dans les arhythmes cardiaques par intoxication à l'imipramine (Tofranil) chez l'enfant. Union Med Can 103:1223-1225, 1974

11. Callaham M: Tricyclic antidepressant overdose. JACEP 8: 413-425, Oct 1979

12. Hagerman GA, Hanashiro PK: Reversal of tricyclic-antidepressant-induced cardiac conduction abnormalities by phenytoin. Ann Emerg Med 10:82-86, 1981

Ascorbic Acid and Nutrition

To the Editor: I am writing about the article by Richard Vilter, MD, "Nutritional Aspects of Ascorbic Acid: Uses and Abuses" in the December 1980 issue.[1] It is extremely well written and will certainly serve as a classic in the field, as our medical attention is drawn more and more to the apparent important aspects of nutrition and nutritional deficiency state. I would take issue with only a few points in the article.

First, one need only assess the incidence of false teeth in our country to ascertain whether Dr. Irwin Stone's hypothesis of very prevalent chronic subclinical scurvy has any merit.

Also, I reviewed references 73, 74, 75, 76, 78 and 80 from the article. In reading these review articles and original works, it becomes very evident that no type of blood testing to determine the at-risk population among those given vitamin C was used. Truly this is a breach of good scientific study. Until a reliable method of determining accurately serum vitamin C levels and pertinent factors is used, we will not be able to determine an at-risk group of persons, nor will we be able to assess accurately the efficacy of any dose of ascorbic acid, by whatever route applied, in the treatment of common colds.

To date we have tested 80 patients with a request for serum vitamin C levels. This has usually given us the reduced vitamin C, or ascorbic acid, content of the blood. I have found no specific trend according to this technique. My practice is composed mainly of chronic debilitated orthopedic pain patients.

Recently, we tested 30 patients according to the technique indicated by Irwin Stone.[2] According to the "morbidity index" that he has defined, most of our patients have demonstrated values in the range of the "survived" or "convalescent" serum levels. The results that we have obtained seem to corroborate, on a preliminary basis, the fact that our patients are indeed clinically debilitated. There are other nutritional factors that we are presently assessing. It is my impression that Dr. Stone's morbidity index at least gives us a standard from which to compare possibly normal and abnormal patients. I am sure that this represents merely a step in the right direction, however. I believe that other measurements will be defined in the future so that we may be able to determine more accurately the specific group at risk from the low vitamin C levels in the blood.

MICHAEL S. MARGOLES, MD
San Jose, California

REFERENCES

1. Vilter RW: Nutritional aspects of ascorbic acid: Uses and abuses (Nutrition in Medicine). West J Med 133:485-492, Dec 1980

2. Stone I: The Healing Factor—Vitamin C Against Disease. New York, Grosset and Dunlap, Publisher, 1972

Hypokalemia in the Syndrome of Inappropriate Secretion of Antidiuretic Hormone

To the Editor: The cause of hypouremia[1] and hypouricemia[2] in the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) has been thought to be increased urinary losses of the above metabolites. I wish to report the association between hypokalemia and severe hyponatremia where the hypokalemia probably reflected increased urinary losses.

Eight cases were studied in which hyponatremia of less than 110 mEq per liter developed during patients' hospital stays and in which the criteria for the diagnosis of SIADH[3] also were fulfilled. Four patients had malignant lesions (lung two, brain one, breast one), two had tuberculosis, one patient presented with pneumonia and the last patient had a cerebrovascular accident. All patients received at least five liters of 5 percent glucose in water intravenously during the first seven-day period in hospital. Serum sodium and potassium levels were measured at least four times from the time of admission to the time the serum sodium value fell below 110 mEq per liter. The results showing the change in electrolyte concen-

trations are shown in Figure 1. Table 1 shows the percentage decrease in serum sodium and potassium. The decrease in serum sodium and potassium seen during the first five days can be explained by dilution. The pronounced drop in serum potassium values seen after serum sodium levels fell to below 110 mEq per liter is greater than what can be accounted for by dilution alone. This can be explained by the fact that severe hypotonic volume expansion can lead to a rise in aldosterone levels.[4] This could then augment renal potassium losses. Urine potassium values seen in four of the above patients on days six and seven were 26, 31, 33 and 36 mEq per liter, respectively.

The importance of the above finding is that the dangers of severe hypokalemia may be superimposed on the clinical problems encountered with severe hyponatremia in patients with SIADH.

AMIN A. NANJI, MD
Division of Clinical Chemistry
Vancouver General Hospital
Vancouver, British Columbia

TABLE 1.—*Percentage Decrease in Mean Sodium and Potassium Concentrations in the Eight Patients*

	Percent Decrease in Concentration		
	*Days 2-3**	*Days 4-5**	*Days 6-7**
Sodium	7.3	8.7	8.6
Potassium	9.3	8.1	29.0

*Reflects percentage decrease from previous electrolyte result.

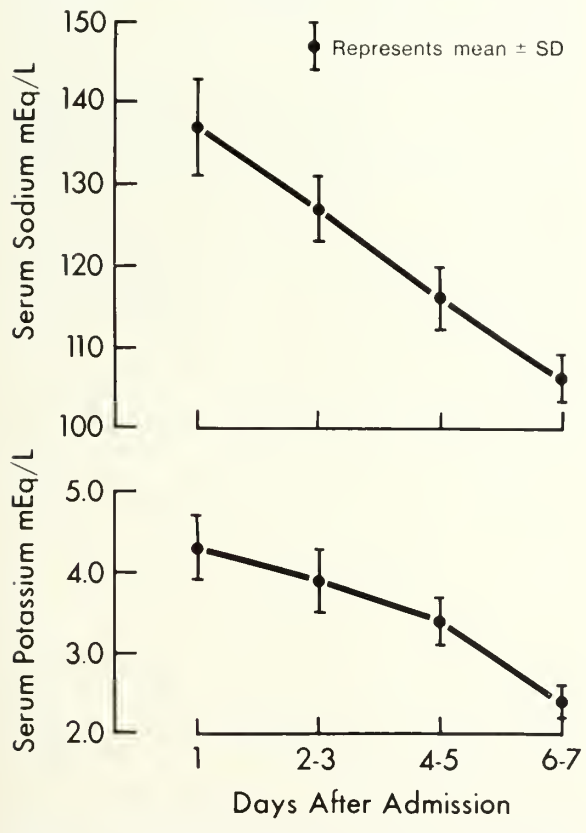


Figure 1.—Changes in serum sodium and potassium levels during the study period.

REFERENCES

1. Decaux G, Genette F, Mockel J: Hypouremia in the syndrome of inappropriate secretion of antidiuretic hormone. Ann Intern Med 93:716-717, 1980
2. Beck LH: Hypouricemia in the syndrome of inappropriate secretion of antidiuretic hormone. N Engl J Med 301:528-530, 1979
3. Barrter FC, Schwartz WB: The syndrome of inappropriate secretion of antidiuretic hormone. Am J Med 42:790-806, 1967
4. Cohen JJ, Huller HN, Smithline N, et al: The critical role of the adrenal gland in the renal regulation of acid-base equilibrium during chronic hypotonic expansion. J Clin Invest 58:1201-1208, 1976

Medical Records as Instruments of Patient Care

TO THE EDITOR: In the February issue[1] Samuel E. Spital, Esq., reinforces the need for detailed record keeping as one of "the realities of practicing medicine in the 1980's."

It would be ostrich-like to argue the facts of life in our current legal climate. However, occasionally one must recall the purpose of record keeping. A written record is kept so that a physician may recall the pertinent medical facts about a patient. The record, therefore, represents a memory jog for the physician who obviously cannot keep all facts about all patients in his head, and a means of communicating the patient's medical history to another physician, should the occasion arise.

The facts of life of the second half of the 20th century, however, require that we keep records not to benefit the patient, nor to inform our colleagues, but to protect us from attorneys and negotiate for third party reimbursement. Therefore, entries into the medical record frequently contain items of no medical significance. Records have become an exercise in creative writing or a legal document. As such, it is almost impossible to make a record which is not penetrable by a clever plaintiff's attorney or deniable for payment by an underfunded agency. As physicians, we are not trained in law and thus are amateurs trying to create legally defensible documents.

The informed consent that all surgical patients sign in hospitals is a case in point. Such instruments represent words in a game played between the hospital's attorneys and the plaintiff's lawyers. They are rarely understandable to an average

patient and usually penetrable by even the most modest of attorneys. However, the ritual signing continues.

One can only hope that in some future paradise, when reason replaces our current greed-driven civil jurisprudence and the Alice in Wonderland of bureaucratic overseers, then medical records can return to being instruments of patient care and not documents of legal defense or financial negotiation.

GARRY S. BRODY, MD
Downey, California

REFERENCE

1. Spital SE: The importance of making precise medical records in the 1980's (Correspondence). West J Med 134:169-170, Feb 1981

Correction: Use of Steroids in Burn Care

TO THE EDITOR: I wish to call to your attention a significant typographical error in my article "Advances in Burn Care," which appeared in the March issue.[1] Under the section "Smoke Inhalation" the article states, "steroids have been shown to reduce mortality . . . ." This sentence should read, "administration of steroids has *not* been shown to reduce mortality . . . ." The basis for this statement is an excellent double-blinded prospective study by Dr. Joseph Moylan at Duke University. In his study both the mortality rate and the infectious complication rate was significantly higher in patients who had received steroids following smoke inhalation and cutaneous burns.[2] Based on this study I cannot advocate the use of steroids in patients with combined burns and smoke inhalation. I trust your readers will be made aware of this correction.

DAVID M. HEIMBACH, MD
Director, Burn Center
University of Washington Burn and Trauma Center
Harborview Medical Center
Seattle

REFERENCES

1. Heimbach DM, Engrav LH, Marvin JA: Advances in burn care (Information). West J Med 134:274-279, Mar 1981
2. Moylan JA, Chan CK: Inhalation injury—An increasing problem. Ann Surg 188:34-37, Jul 1978

Platelet Dysfunction and Migraines

TO THE EDITOR: I wish to commend Drs. Huebsch and Harker for their timely review of platelet function disorders in the February 1981 issue.[1] I am curious, however, why they neglected to include the role of platelet dysfunction in the pathogenesis of the migraine syndrome.

The first to show an association of increased platelet aggregability to migraine were Kalendovsky and Austin[2] in 1975. Subsequently, Deshmukh and Meyer[3] studied platelet function in migraineurs. They found that migraineurs had a significantly lower circulating microemboli index and higher aggregation responses to adenosine diphosphate (ADP) when compared with controls. Specifically, platelet adhesiveness to glass beads and platelet aggregation responses to ADP, epinephrine, thrombin and serotonin, increased during the prodromal phase of the migraine attack. During the headache phase, adhesiveness increased and aggregation in response to ADP and epinephrine decreased significantly. They concluded that previously observed platelet serotonin changes associated with migraine[4,5] paralleled their findings on platelet changes.

In the same year, using optic density methods, Couch and Hassanein[6] tested platelet aggregation responses to various concentrations of ADP in patients with migraine and in matched controls. They found that compared with controls, migraineurs had platelet hyperaggregability and following aggregation a decreased tendency to disaggregate. Since they could find no correlation of platelet changes to severity of headache attacks, Couch and Hassanein[6] suggested that platelet hyperaggregability was a concomitant feature of the migraine disorder independent of the headache state.

Gawel and co-workers,[7] in a controlled study, further showed a significant rise in serum beta thromboglobulin (BTG) in patients during migraine attacks but not during headache-free periods. They concluded that the platelet release reaction occurs during the headache phase of migraine; a conclusion somewhat different from that of Couch and Hassanein.[6]

Concerning another pathway in migraine involving platelets, Sandler and co-workers[8] and Sicuteri and associates[9] found a deficiency of platelet monoamine oxidase (MAOB) in some migraineurs.

LEE KUDROW, MD, Editor
Headache Update
Director, California Medical Clinic for Headache
Encino, California

REFERENCES

1. Huebsch LB, Harker LA: Disorders of platelet function—Mechanisms, diagnosis and management (Medical Progress). West J Med 134:109-127, Feb 1981
2. Kalendovsky Z, Austin JH: "Complicated migraine," its association with increased platelet aggregability and abnormal plasma coagulation factors. Headache 15:18-35, 1975
3. Deshmukh SV, Meyer JS: Cyclic changes in platelet dynamics and the pathogenesis and prophylaxis of migraine. Headache 17:101-108, 1977
4. Sicuteri F, Testi A, Anselmi B: Biochemical investigations in headache increase in the hydroxyindoleacetic acid excretion during migraine attacks. Int Arch Allergy Appl Immunol 19:55-58, 1961

5. Anthony M, Hinterberger H, Lance JW: The possible relationship of serotonin to the migraine syndrome, *In* Friedman AP (Ed): Research and Clinical Studies in Headache—Vol 2. Basel, Karger, 1969 pp 29-59

6. Couch JR, Hassanein FR: Platelet aggregability in migraine. Neurology 27:843-848, 1977

7. Gawel M, Burkitt M, Rose FC: The platelet release reaction during migraine attacks. Headache 19:323-327, 1979

8. Sandler M, Youdim MBH, Hanington E: A phenylethylamine-oxidising defect in migraine. Nature (London) 250:335-337, 1974

9. Sicuteri F, Buffoni F, Anselmi B, et al: An enzyme (MAO) defect on platelets in migraine. Res Clin Stud Headache 3:245-251, 1972

* * *

Dr. Harker Replies

To the Editor: Thank you for the courtesy of giving us the opportunity to reply to the letter from Dr. Kudrow regarding increased platelet aggregability in association with migraine.

As pointed out in the introduction to the review by Dr. Huebsch and myself, we limited the discussion to clinically significant defects in platelet function, their pathophysiology, diagnosis and management. We did not include any disorders of increased platelet aggregability or the role of platelets in thrombosis or atherogenesis. Therefore, it would have been inappropriate to include a discussion on migraine.

LAURENCE A. HARKER, MD
Professor of Medicine
Division of Hematology
Harborview Medical Center
Seattle

Accidental Hypothermia: Hypoglycemia or Hyperglycemia

To the Editor: We read with interest the article "Hypoglycemia and Accidental Hypothermia in an Alcoholic Population," in the August 1980 issue, which showed that 41 percent of Dr. Fitzgerald's hypothermic patients were hypoglycemic.[1] These data were surprising to those of us who have found the opposite results in our series of hypothermic patients. We are not sure that the incidence of hypoglycemia may be this high; in fact, in a review of 39 hypothermic patients, 34 of whom had impaired liver function or history of chronic alcoholism (or both) only 1 patient had a blood glucose level below 58 mg per dl.[2] All of our patients were hyperglycemic with glucose levels as high as 1,278 mg per dl.[3] None of our patients had a history or physical findings to suggest hepatic dysfunction. Hypothermia has multiple effects on the body's physiology. A recent review discusses the role of hypothermia producing hyperglycemia.[4]

We would suggest that there may be two dissimilar groups of hypothermic patients. One group may be characterized by the alcoholic patients with severe liver impairment and depleted glycogen stores with resultant impaired gluconeogenesis who therefore present with hypoglycemia. The other, and far larger group, would contain all those patients with relatively healthy livers who during their episodes of hypothermia may in fact be hyperglycemic to a pronounced degree. In her conclusions Dr. Fitzgerald suggested empirically treating hypothermic patients with an intravenous bolus of 50 percent glucose solution. We believe the use of a capillary blood glucose determination by a finger stick method in the emergency room would quickly and inexpensively identify these two groups. This would be preferable to empirically treating all hypothermic patients as having hypoglycemia.

PHILIP ALTUS, MD
JACK W. HICKMAN, MD
Department of Internal Medicine
University of South Florida
College of Medicine, Tampa

REFERENCES

1. Fitzgerald FT: Hypoglycemia and accidental hypothermia in an alcoholic population. West J Med 133:105-107, Aug 1980

2. Weyman AE, Greenbaum DE, Grace WJ: Accidental hypothermia in an alcoholic population. Am J Med 56:13-21, 1974

3. Altus P, Hickman JW, Pina I, et al: Hypothermia in the Sunny South. So Med J 73:1491-1492, 1980

4. Besdine R: Accidental hypothermia; the body's energy crisis. Geriatrics 34:51-59, 1979

* * *

Dr. Fitzgerald Replies

To the Editor: Doctors Altus and Hickman express surprise at the high incidence of hypoglycemia in my alcoholic hypothermic patients. It was the same astonishment that led me to publish the series. Hypothermia may indeed lead to hyperglycemia in some patients. As tissue temperature falls, glucose consumption by cells decreases.[1,2] Pancreatic insulin release[3] and tissue sensitivity to insulin[4] may be blunted.

Four of our patients had an admission diagnosis of cirrhosis. One would expect, if the hypothesis forwarded by Doctors Altus and Hickman were correct, that these patients would be the most likely to be hypoglycemic. Yet in only one of these four was there a serum glucose value in the hypoglycemic range (37 mg per dl). The case has been made, in fact, that liver dysfunction may significantly contribute to hyperglycemia in hypothermic patients.[1] It is difficult to predict either from the published literature or the patient's past history whether or not a given hypothermic individual patient will be hyperglycemic or hypoglycemic. At the same time hypothermia may ob-

secure physical diagnostic findings characteristic of hypoglycemia or hyperglycemia.

Because I am unaware that the capillary blood glucose determination by fingerstick method has been studied for accuracy in the hypothermic patient (and one might expect an enzymatic determination to be altered by hypothermia), and because I believe there to be no significant clinical harm done in giving a one-time bolus of 50 percent glucose solution intravenously (even in a hyperglycemic patient), I would continue to recommend empiric therapy with intravenous administration of glucose in all hypothermic patients. Clearly, such therapy should not obviate careful and continuous monitoring and observation of hypothermic patients throughout the period of rewarming, during which period dramatic changes in glucose levels might be anticipated.

FAITH T. FITZGERALD, MD
Department of Internal Medicine
University of California, Davis, School of Medicine
Davis, California

REFERENCES

1. Henneman DH, Bunker JP, Brewster WR Jr: Immediate metabolic response to hypothermia in man. J Appl Physiol 12: 164-168, 1958

2. Fuhrman FA, Crismon JM: The influence of acute hypothermia on the rate of oxygen consumption and glycogen content of the liver and on the blood glucose. Am J Physiol 149:552-560, 1947

3. Curry DL, Curry KP: Hypothermia and insulin secretion. Endrocrinology 81:750-755, 1970

4. Bickford AF, Mottram RF: Glucose metabolism during induced hypothermia in rabbits. Clin Science 19:345-359, 1960

Appropriateness Review

TO THE EDITOR: The comments in the March issue by Dr. Howard Lang[1] about Appropriateness Review provisions of Public Law 93-641 are valid. Fortunately, there is so much question about the efficacy of PL 93-641 that many changes, and perhaps even repeal, may be anticipated in the next two years. Appropriations have been so reduced that many Health Systems Agencies (HSA) have had to reduce staff by as much as a third. Recognizing this, the Bureau of Health Planning of the US Department of Health and Human Services is now seriously considering "functional" exclusion of Appropriateness Review (AR) as a local, and therefore a state level, activity.

In these circumstances, it is difficult to predict what will happen in the various states. Where state decertification laws are already on the books, giving sanctions not provided by Congress, it is likely that AR will continue, in some form, under state direction. Fortunately, California does not have a decertification law.

The California Medical Association (CMA), in conjunction with the California Hospital Association (CHA), is considering the best approach to enabling legislation, which if not passed this fall, will place California in jeopardy of losing $600 million per year in Public Health Service money. There is no question that the CMA proposed enabling legislation will have *sunset* provisions to allow for possible congressional repeal; it should be realized that if the CMA/CHA bill had not been introduced last year, Governor Brown would have signed the administration bill, and we would now be saddled with all of the regulations and rationing cited in Dr. Lang's letter.

Planning for the future is necessary, and CMA and the American Medical Association have always supported this. Regulation to "correct" the past, present and future is what the current law is about. Repeal seems quite more likely now and the AMA House of Delegates has instructed its councils to develop principles of planning which will preserve the integrity of the medical profession in any future voluntary and local health planning initiatives.

ROY R. DEFFEBACH, MD
Redwood City, California
Chairman, Committee on Health Planning and Resources Development
California Medical Association

REFERENCE

1. Lang HL: Appropriateness review: An overview (Correspondence). West J Med 134:265-266, Mar 1981

Refer to: Thorburn KM: Croakers' dilemma—Should prison physicians serve prisons or prisoners? (Medical Ethics). West J Med 134:457-461, May 1981

Croakers' Dilemma

Should Prison Physicians Serve Prisons or Prisoners?

KIM MARIE THORBURN, MD, *San Francisco*

PRISON PHYSICIANS may be asked to evaluate inmates' physical ability to withstand corporal punishment and, periodically, to determine whether punishment can be continued.[1] The participation of physicians in punishment and execution of prisoners is an extreme example of a dilemma facing all physicians employed by authoritarian and punitive systems to which their patients are committed. A prison physician's practice requires actions that are in the interests of either the prison or the prisoners, but sometimes unfavorable to the other. In fact, the dilemma of whose interest physicians are serving permeates nearly every aspect of prison medical practice. When physicians' actions cannot be in the interests of both, whom shall they serve: the prison or the prisoner?

Medical ethics dictate that patients are physicians' foremost responsibility, so it would seem that there is no dilemma. Yet it may be inherently impossible for prison physicians to meet their responsibility to patients when the institution seeks complete authority over their patients' lives.[2] Inmates often charge collusion between physicians and prison officials, and even the term *croaker,* which many inmates call doctors, implies disdain for their physicians' position.

Leo L. Stanley was known as San Quentin's Chief Croaker for about 40 years. His career began there in 1913. After 27 years in the institution he wrote his story in *Men at Their Worst* and revealed not only a progressive attitude toward prison medicine but also insight into his position and relation with the inmates:

> I am possibly the most hated official in San Quentin and I know it. Much of the animosity that is bound to develop in a caged man's mind is focused on the medical department. My position is a vulnerable one. If a prisoner doesn't get the food he likes or the treatment he feels he deserves, or if he fails to 'make pogey,' [get admitted to the hospital] he blames me.[3]

Medical Treatment Versus Custodial Functions

Custodial functions including maintaining control and administering punishment are prison priorities, but these functions may directly interfere with medical treatment. There are many examples of conflicts between medical and custodial functions in routine practice.

In maximum security areas inmates may be locked in their cells or allowed to leave them only when manacled or closely guarded. Manacled arms or legs prevent proper examination. There is also lack of privacy which is necessary for confidentiality in a doctor-patient relationship. Inmate access to medical care is dependent on cooperation by those in authority even in minimum security areas. Guards may interfere by not releasing inmates to sick call or by not transporting them to medical appointments. Such interference may be unintentional through subjugation of medical care to custodial functions, or it may be intentional. When an inmate is injured in a fight with other inmates or guards, prison authorities may wish to punish the offender by withholding treatment.

Medically important information may be incriminating, and records usually are obtained by

Dr. Thorburn is Staff Physician, Neumiller Hospital, California State Prison at San Quentin and Clinical Instructor, Department of Medicine, University of California, San Francisco.

The opinions contained herein are those of the author and are not to be construed as the official views of the San Quentin prison administration.

Reprint requests to: Kim M. Thorburn, MD, Neumiller Hospital, California State Prison at San Quentin, Tamal, CA 94964.

authorities without patient release. The chief psychiatrist at Soledad prison was fired in 1971 for insubordination when he refused to give records to the warden.[4] Prisoner access to records in the New Mexico state prison riots had devastating consequences.[5]

Nonmedical Requests

There are duties thrust upon prison physicians which may create conflicts and weaken the doctor-patient relationship. Special diet requests, whether for medical reasons or personal preferences, usually require approval by physicians. Diets are not easily provided by prison kitchens, and if physicians were to order diets for everyone, a kitchen staff would become angry. However, when physicians tell patients special diets cannot be provided, they feel trapped because they know that only doctors can approve diets. This is one example of the many nonmedical requests that burden prison physicians who are attempting to solve the dilemma of meeting their responsibility to patients.

Prison physicians trying to practice by the principle that patients are their primary concern may inadvertently contribute to prison corruption. One of doctors' foremost functions is alleviation of suffering, yet overprescription of such medications as sedatives or analgesics must also be avoided because of the high potential for abuse. Prisoners are allowed only small amounts of money for commissary items, and a variety of medications have great value in barter. Cigarettes are the most common item for exchange, but pills are also used as currency when they are available. Even careful prescription of medications with obvious potential for abuse does not preclude their misuse. Antihistamines, sympathomimetics and phenothiazines are misused as well.

Physicians who grant all inmate requests for special diets and other commodities often find that most of their time is spent in answering demands for nonmedical goods. These physicians will find inmates coming to sick call in order to leave their cells or to avoid work. Prisoners may use medical care as a bargaining point saying, for example, that they will refuse treatment unless unnecessary drugs are prescribed or their custody status is changed.

Malingering

Malingering and manipulation by prisoner patients are common and are part of the physicians' dilemma. The benefits of sick call and the hospital include increased mobility and prescriptions, and misdiagnosis of malingering can contribute to prison corruption. Yet prisoner health concerns may be sincere. Hours of inactivity encourage prisoners to focus attention on minor symptoms, and the fear of dying behind bars is universal.

Special Functions

Sometimes prison physicians are asked to perform special functions that require medical skills but are not part of routine practice, and sometimes this involves carrying out procedures on unwilling patients. Forced body searches, force-feeding and attendance or participation in capital punishment are examples.

Forced Examinations

Physicians may be asked to carry out forced examinations for illicit drugs or weapons. Use of illicit drugs is a prevalent problem in prisons and the complications of abscesses, overdoses, hepatitis and endocarditis require medical attention. Frequently, physicians are needed to care for victims of stabbings and gunshot wounds. The import of drugs or weapons via the vagina or intestinal tract is common.

Physicians cannot justify forced examination to search for drugs even though prevention of access to illicit drugs protects the community's health. Drugs carried in body cavities can be recovered by custodial staff. Lay people are easily taught techniques of vaginal examination, and swallowed or rectally held contraband can be retrieved from cells with traps in toilets.

Weapons harbored vaginally or rectally require removal by a physician to avoid harm to the individual prisoner, unlike recovery of illicit drugs from body cavities, which can be done safely without medical intervention.[6] Inmates suspected of carrying weapons are often combative, and forcible extraction of a metallic, sometimes sharp, object endangers vital body structures. Physicians are sometimes asked to diagnose the condition using x-ray films, and general anesthesia may then be necessary for safe removal of concealed objects from resisting patients.

Force-Feeding

Prison physicians may be requested to force treatments on malnourished hunger-striking inmates. Hunger strikes are a traditional means used by prisoners to convey political messages.

Gravely malnourished hunger strikers present

a conflict between physicians' responsibility to protect health and life and their obligation to respect human freedom.[7] Physicians must decide, without influence from authorities, whether a particular hunger strike is a voluntary act, such as commitment to a political statement, or a manifestation of psychopathology. When a psychotic Black Muslim, for example, refuses nourishment because all the food is "smeared in swine grease" it may be difficult to decide whether this is a political statement or a delusion.

When the decision to hunger strike is rational, force-feeding is a form of assault. Treatments are usually not forced on free patients making rational decisions. Eventually starvation prevents a sound mind. The authorities may then urge force-feeding because hunger strikers' deaths may have serious and far-reaching political consequences. Perhaps a more humane solution than force-feeding was Britain's Cat and Mouse Act, which was enacted to deal with hunger-striking suffragettes. Under this law hunger strikers were released from prison, then reincarcerated when again fit.[8]

Attendance at Executions

Required attendance at executions is an extreme example of the dilemma because physicians are serving only the prison employer. Under some state laws, physicians must be present to pronounce the prisoner dead and to treat medical conditions among members of the audience. Their presence does not make the act of capital punishment more humane and, in fact, lends tacit approval to the act. Physicians' work is to save lives, not to take them.

Mandatory attendance at executions is a dilemma that, conceivably, could be compounded by a prisoner's paradoxic request that physicians be present. Answering this request is not simple. Those who express concern that physicians' presence guarantees a rapid, humane death should be assured that this is the executioner's, not the physicians', function. Physicians care for the living—attending the prisoner up to the death chamber door, but not beyond. Physicians care no less for life on death row, although there is a great sense of irony in examining and treating the condemned.

The physicians' role in executions is further complicated by the death by lethal injection laws which have been enacted by several states. Medical participation in such executions, at least as advisors, may be requested. Many physicians* feel such participation in executions is unethical.[9,10]

Prison Physician-Patient Relationship

Prisoner patients are affected by the croakers' dilemma in two ways: First, prisoners find that they are expected to confide in doctors they have not chosen, who work for the institution which punishes their infractions. Second, practicing medicine according to community standards means allowing informed consent. Yet prison provides limited options.

Medical histories may include information about misbehavior and broken rules. Prisoners may be reluctant to reveal such information to prison physicians who, in their minds, represent authority. Concern about the physicians' position may turn into general mistrust of the quality of medical care.

Informed Consent

Prisoners' options regarding medical care are limited, making informed consent impossible when compared with the situation of patients outside of prisons.[11] Prisoners have no choice about who provides their care unless they can afford doctors from outside. Their option is simply whether or not to receive the form of care provided by the prison.

The emphasis on choice by the medical department may have unfortunate consequences. Prisoners seem to express resentment for their closely controlled lives by frequently refusing treatments urged by their doctors.

An interesting aspect of informed consent arises when communicating with prisoner patients' families. Incarceration of a family member may cause a sense of shame. Prisoner permission is necessary, whenever possible, before talking to a family member and information must be strictly limited to medical problems.

Prisoner Experimentation

The ability of prisoners to give informed consent has been central to the debate about prisoner experimentation. In 1976 the Department of Health, Education and Welfare banned all prison research funded by its grants[12] after the Congress-

*EDITOR'S NOTE: The House of Delegates of the American Medical Association in 1980 adopted the following recommendation of the AMA Judicial Council: "(1) An individual's opinion on capital punishment is the personal moral decision of the individual. (2) A physician, as a member of a profession dedicated to preserving life when there is hope of doing so, should not be a participant in a legally authorized execution. (3) A physician may make a determination or certification of death as currently provided by law in any situation."

mandated National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research recommended limitation of prison experimentation to that with therapeutic outcomes.[13,14] The Food and Drug Administration is also considering prohibiting drug company research in prisons.[12]

Biomedical research in prison has been popular because the subjects' services are cheap and readily available, and the subjects live in a closed, well-controlled environment. Stanley was an advocate of prison research for these reasons.[3] Long before isolation of testosterone, Stanley carried out more than 10,000 "testicular transplants." Stanley's work was vociferously opposed when a newspaper reporter found that the testes in one case were removed at the autopsy of a hanged man.[3] It was not until recently, however, that public outcry almost halted prison research. Experiments have included intentional infection of inmate *volunteers* with malaria and other potentially infectious agents, including leukemic cells, and deliberate addiction to drugs. In one study a hepatitis epidemic due to poor venipuncture techniques during experimentation horrified the public.

Opponents of prison research argue that prisoners cannot give informed consent when deciding whether to participate in research.[16] In fact, some of the most outspoken advocates of prison research are prisoner and exprisoner participants who point out the improvement in prisoner lives through the benefits of research participation.[17-19] To be a research subject means better pay than other prison jobs provide, early parole, change in environment and medical care. Such benefits may make well-informed decisions about the risk of participation in experiments difficult.

A group at the Health Policy Program of the University of California, San Francisco, suggested "inverse-risk rating" as a method to allow informed consent by prisoners participating as subjects in biomedical research. Experiments are judged in terms of risks and dangers to subjects, and higher-risk procedures are carried out only in institutions with relatively greater freedom.[20]

Can the croakers' dilemma of having two masters be solved? There is obviously no general answer that can be applied to all of the situations described.

The solutions to conflicts with custody procedures interfering with routine medical practice are straightforward. Courts have ruled that withholding medical care from prisoners is cruel and unusual punishment prohibited by the Eighth Amendment,[21] so there is legal support for alteration of regulations interfering with medical care. At times high-security procedures are necessary for prison safety, and certain restraints that may interfere with usual medical procedures are prudent. But punitive regulations that prevent adequate medical care are not acceptable. The routine medical needs of prisoner patients have priority, and if proper care cannot be provided in the prison setting, admission to a medical facility is necessary.

Declaration of Tokyo

Prison authorities should not dictate medical decisions. The World Medical Association wrote the Declaration of Tokyo at its 29th assembly in 1975 "concerning torture and other cruel, inhuman or degrading treatment or punishment in relation to detention and imprisonment,"[22] which provides ethical guidelines for prison physicians. Recognizing the conflicts that confront prison physicians, declaration 5 says, "A doctor must have clinical independence in deciding upon the care of a person for whom he or she is medically responsible."[22]

Independence in clinical decision-making applies to all aspects of routine medical care. Who sees the doctor is a medical decision, and patients are triaged by ancillary health personnel, not guards. Physicians' recommendations about treatments should not be affected by the regulations or demands of prison authorities. Declaration 8 states, "The doctor shall in all circumstances be bound to alleviate the distress of his fellow men, and no motive—whether personal, collective or political—shall prevail against this higher purpose."[22] Treatment should not be withheld for punishment, although careful evaluation of patients and fair, consistent prescribing practices are necessary to prevent prescription drug abuse. Finally, medical information is confidential and should be released only with patient permission. Authorities must not have free access to medical records.[11]

Worldwide, the question of force-feeding hunger-striking inmates is controversial. While forced treatment is an assault, the death of a hunger striker might be murder.[7] Declaration 6 favors free choice by hunger strikers:

> Where a prisoner refuses nourishment and is considered by the doctor as capable of forming an unimpaired and

rational judgment concerning the consequences of such a voluntary refusal of nourishment, he shall not be fed artificially. The decision as to the capacity of the prisoner to form such a judgment should be confirmed by at least one other independent doctor. The consequences of refusal of nourishment shall be explained by the doctor to the prisoner.[22]

Physicians who oppose capital punishment might find support from the Declaration of Tokyo in refusing to attend or participate in executions. The Declaration proscribes condonement, attendance or participation in "the practice of torture or other forms of cruel, inhuman or degrading procedures."[22]

Physicians may slowly build inmate patient trust by respecting the confidentiality of the doctor-patient relationship; however, allowing informed consent with free choice among options is difficult in prison. The options may be limited, but prisoners should be offered a choice. For example, prisoners suspected of using drugs are asked to submit to blood or urine tests. They are faced with the choice to allow the tests or to be punished, sometimes with additional charges. In cases where inmates are suspected of harboring weapons, diagnosis is made with radiographs. Ideally, patients should be informed about radiation risks and allowed a choice between x-ray and ultrasonographic procedures. Forced feeding is another issue where informed consent might take an unusual form. The prisoner is told the risks, including death, of not eating and allowed to choose whether or not to break the fast when following the Declaration of Tokyo recommendations. In places where forced feeding of hunger strikers is practiced, the risks of tube feeding must be understood and the prisoner allowed to choose between it and eating.

Conclusions

Prison medicine is a rewarding practice despite its frustrating conflicts. There are many reasons for striving toward high quality health care in prisons besides legal and humanitarian rights of prisoners. Crowded, often unsanitary, living conditions can be public health hazards. Preventive care and management of chronic illnesses may save costly catastrophic disease. The physician's role as an educator in describing and carrying out medical treatments can be rehabilitative by improving prisoners' self-awareness and self-image. Suffering by prisoners can be immense, with prolonged separation from family and friends in degrading living conditions. Physicians and others in the medical department can be benevolent contacts with the outside world as they work to deliver health care. These accomplishments in the course of routine health care delivery provide a sense of fulfillment.

Is there a dilemma for *croakers* forced to choose between service to prisoners or the prison? There will always be conflicts while prisons are violent institutions for punishment, rather than safe houses of detention. The custodial goals of prison authorities often counter the practice of medicine, and physicians may have difficulties when custodial and medical functions overlap. Physicians may sense pressures directing their practice in a prison's authoritarian environment. Prisoner patients with closely controlled lives may find opportunity for manipulation in the medical department's emphasis on choice and options. But there is no dilemma. Patients are doctors' first priority and their interests are foremost—and this principle must guide physicians whenever conflicts arise.

REFERENCES

1. Bowden P: Medical practice: Defendants and prisoners. J Med Ethics 2:163-172, Dec 1976
2. Sissons PL: The place of medicine in the American prison: Ethical issues in the treatment of offenders. J Med Ethics 2:173-179, Dec 1976
3. Stanley LL: Men at Their Worst. New York, D Appleton Century Co, Inc, 1940, pp 98, 241
4. Wright EO: The Politics of Punishment—A Critical Analysis of Prisons in America. New York, Harper and Row, 1973, p 349
5. Marchetto M: The New Mexico riot. San Quentin News 50:2, May 2, 1980
6. Curran WJ: Ethical and legal problems in medical participation in criminal investigatons. N Engl J Med 294:764-765, Apr 1, 1976
7. Lewey L: Force-feeding—A clinical or administrative decision? Can Med Assoc J 116:416,419, Feb 19, 1977
8. Legal Correspondent: Force-feeding in prison. Br Med J 2:823-824, Oct 2, 1976
9. Curran WJ, Casscells W: The ethics of medical participation in capital punishment by intravenous drug injection. N Engl J Med 302:226-230, Jan 24, 1980
10. Perry JC, Chapman CB, Nelson JR, et al: Medical participation in capital punishment (Correspondence). N Engl J Med 302:971, Apr 24, 1980
11. Roy C: Dilemmas of medical ethics in the Canadian penitentiary service. J Med Ethics 2:180-184, Dec 1976
12. Gettinger S, Krajick K: The demise of prison research. Corrections Mag 5:4-9, 13-14, Dec 1979
13. Gregory DR: Research involving prisoners. J Leg Med 5: 53, Jun 1977
14. Branson R: Anatomy of an ethical decision—Prison research: National commission says "no, unless . . ." Hastings Cent Rep 7:15-21, Feb 1977
15. Mitford J: Kind and Usual Punishment—The Prison Business. New York, Vintage Books, 1974, pp 154-157
16. Bach-y-Rita G: The prisoner as an experimental subject. JAMA 299:45-46, Jul 1, 1974
17. Hatfield F: "A sense of purpose." Prison research: The view from inside. Hastings Cent Rep 7:11-12, Feb 1977
18. Travitzky DE: "My own choice." Volunteering at Vacaville. Hastings Cent Rep 7:13, Feb 1977
19. Hatfield F: Prisoner research (Correspondence). JAMA 229:1720-1721, Jul 1, 1974
20. Jonsen AR, Parker ML, Carlson RJ, et al: Biomedical experimentation on prisoners. Review of practices and problems and proposal of a new regulatory approach. Ethics Sci Med 4: 1-28, 1977
21. Holder AR: Prisoner's right to treatment and communication. JAMA 231:198, Jan 13, 1975
22. Council of the World Medical Association: Declaration of Tokyo. World Med J 22:90-91, Oct 1975

WYOMING State Medical Society

WSMS Annual Meeting and Scientific Program Schedule

JUNE 22-26, 1981 • JACKSON, WYOMING • AMERICANA SNOW KING HOTEL

MONDAY, JUNE 22

8:00 am

PETER F. KOHLER, MD

Professor of Medicine, Head of Clinical Immunology, University of Colorado School of Medicine, Denver, Colorado

Dr. Kohler will discuss recent developments in the field of clinical immunology and the ramifications for patient care. His talk will include an introduction to immunologic aspects of recurrent infections. He will also discuss immune complex injury in vasculitis and connective tissue disorders.

10:45 am to 12:00 noon

HARMON J. EYRE, MD

Associate Professor of Medicine, Division of Hematology and Oncology, Department of Internal Medicine, University of Utah College of Medicine, Salt Lake City, Utah

Under the sponsorship of the American Cancer Society and the Whedon Cancer Detection Foundation Dr. Eyre will present the current developments and the potential uses of interferon.

TUESDAY, JUNE 23

8:00 am

PETER G. TUTEUR, MD

Associate Professor of Medicine, Pulmonary Disease Division, Washington University School of Medicine, St. Louis, Missouri

Dr. Tuteur will present a discussion of recent developments related to the etiology, diagnosis, prevention and management of toxic shock syndrome. At 9:00 AM Dr. Tuteur will discuss ambulatory therapy for the patient with chronic obstructive pulmonary disease, adult respiratory distress syndrome and the approach to the patient who is wheezing acutely.

11:00 am to 12:00 noon

PANEL DISCUSSION

Present cases of patients with respiratory problems from your practice to the panel of experts. Dr. Tuteur will be joined by the following Wyoming physicians: Darryl Bindschadler, MD, Harmon Davis, MD, Wesley Hiser, MD, and Donald Smith, MD.

WEDNESDAY, JUNE 24

8:00 am to 12:00 noon

JOSEPH B. TRAINER, MD

Clinical Professor of Preventive Medicine and Public Health, University of Oregon Health Sciences Center, Portland, Oregon

Special hazards and rewards of the medical marriage will be Dr. Trainer's subject, including a discussion of special stresses of the physician's life, why we behave like sexual people and the most frequent sexual problems.

1:30 pm

WSMS HOUSE OF DELEGATES OPENING SESSION

THURSDAY, JUNE 25

8:00 am to 12:00 noon

ARTHUR H. HAYES, JR, MD

Commissioner of Food and Drugs, US Food and Drug Administration, Rockville, Maryland

Dr. Hayes will discuss some of the newer chemotherapeutic agents, their monitoring and the ramifications of their use. The morning session will conclude with a presentation by Dr. Hayes on the clinical significance of the dynamics and kinetics of drug-drug interactions.

1:30 pm

WSMS REFERENCE COMMITTEE MEETINGS

FRIDAY JUNE 26

8:00 am

ROBERT BUCKLIN, MD, JD

Deputy Medical Examiner, Los Angeles County, California

Dr. Bucklin's presentation on the medical aspects of the crucifixion of Christ (as disclosed by the Shroud of Turin) will include comments on his 1978 visit to Turin, Italy, and his scientific studies of the cloth.

9:00 am

DAVID N. SUNDWALL, MD

Physician Advisor to US Senate Committee on Labor and Human Resources, Washington, DC

Dr. Sundwall will discuss Reagan Administration health policies and their impact on physicians and the practice of medicine.

10:45 am to 12:00 noon

MAYNARD V. OLSON, PhD

Assistant Professor of Genetics, Washington University School of Medicine, St. Louis, Missouri

DNA and RNA recombination and the future potential impact on the practice of medicine will be discussed in this presentation by Dr. Olson entitled "DNA—The Achilles Heel of the Cell?"

1:30 pm

WSMS HOUSE OF DELEGATES CLOSING SESSION

For program, reservations and information contact:

WYOMING State Medical Society

WYOMING STATE MEDICAL SOCIETY
Post Office Drawer 4009
Cheyenne, WY 82001
Telephone (307) 635-2424

Refer to: Goyan J: Fourteen fallacies about patient package inserts (Informed Opinion). West J Med 134:463-468, May 1981

Informed Opinion

Fourteen Fallacies About Patient Package Inserts

JERE GOYAN, PhD, *San Francisco*

EDITOR'S NOTE: *FDA's patient package insert program was stopped in the wake of President Reagan's executive order requiring reconsideration of regulations that might cost at least $100 million, increase product costs or adversely affect competition.*

WHEN I moved to Washington in October 1979 to become Commissioner of the Food and Drug Administration (FDA), I resolved to enter my new responsibilities with an open mind, setting aside my prejudices so that I could more easily separate fact from fiction. I found this exercise quite useful. Many of the perceptions I had of Washington and of FDA were quickly altered by the reality I saw before me. What I learned is that accurate information, even in a community that thrives on media coverage, is at a premium, that it is often necessary to focus afresh on issues.

As Commissioner, the single issue that occupied more of my personal time was patient package inserts or PPI's. Because of my background, reporters and health professionals at every opportunity asked me what I was going to do about the PPI rule that FDA had proposed just before I came to Washington. In the first speeches I delivered, I made it clear what my position was:

- that I believed strongly in patient information;
- that patient package inserts were not necessarily the only way to provide such information, but present knowledge seemed to indicate they were;
- that I would keep an open mind about patient package inserts, but that I believed we needed to proceed to see how they work in a real-world situation, and
- that while this pilot program was going on, we still needed to explore alternatives.

You can imagine my surprise when, in midsummer of 1980, nine months after I arrived at the agency and after I had repeatedly expressed my views on patient package inserts, I still continually was asked, "How do you *really* feel about PPI's?" It became obvious that some people just were not listening, or perhaps did not believe, or did not want to believe, what they were hearing. In any event, on September 12, 1980, in a notice published in the federal government's paper of record, the *Federal Register,* FDA spelled out precisely the pilot program I had been advocating. Patricia Roberts Harris, the Secretary of Health and Human Services, had such a personal interest in the program that she decided to announce it personally at a press conference. I met with representatives of health professional groups right after the press conference to answer questions and explain the program.

The response to our program took essentially three forms. Some believed that FDA was moving too slowly, that we should have proceeded with a massive PPI program at once. Others welcomed our initiative and believed the program had just the right balance of innovation and caution. Still others expressed skepticism about the program or rejected it out of hand.

The key to gaining support for the program, I learned, was simple: explain the reasoning behind it and why we thought it the best direction to take. I have found that people who understood

Dr. Goyan was Commissioner of Food and Drugs, Food and Drug Administration, Rockville, Maryland, at the time this article was written.

He is now Dean of the School of Pharmacy, University of California, San Francisco.

Reprint requests to: Jere Goyan, PhD, Dean, School of Pharmacy, S926, UC, San Francisco, San Francisco, CA 94143.

what we were doing, tended to support it; those who did not understand it, tended to oppose it.

With this in mind, then, I have compiled 14 fallacies about patient package inserts and our proposed program. These fallacies have been distilled from my many conversations with consumers and health professionals about the PPI program.

I ask the readers of this article not necessarily to agree with me but to take a lesson from my experience with Washington and FDA: approach the subject with an open mind and set aside preconceptions. I believe that a clear understanding of the PPI program developed by FDA will lead to support for the concept from most of my colleagues in the health professions.

Fallacy Number One: There is no precedent for this kind of requirement. Actually, the first patient package insert was required by FDA in 1968, when it was recognized, at least implicitly, that some drugs could not be used properly unless certain information was conveyed to patients as well as to prescribers or dispensers. Thus, in June 1968, FDA required that each isoproterenol inhalation drug dispensed to a patient bear a two-sentence warning on the container advising of an association between repeated and excessive use and severe paradoxical bronchoconstriction. FDA required the warning because inappropriate use by patients was actually causing the condition the drug was intended to treat.

Other patient package information was required by FDA as the need emerged, particularly for drugs for which patient choice should be a factor in the prescribing decision. Thus, in June 1970, FDA required that patient information be dispensed with oral contraceptives. In July 1977 FDA required patient information for estrogens. In 1978, when new information became available about orally taken contraceptives, labeling for patients was revised to require more detail. Later, FDA established patient labeling requirements for intrauterine devices (IUD's) and for progestational drug products. Thus, a series of precedents for patient package information date back a dozen years.

Fallacy Number Two: FDA does not have legal authority to require patient package inserts. One test of FDA's legal authority to require PPI's resulted from a suit filed in 1977 against FDA's estrogen patient package insert regulation by the Pharmaceutical Manufacturers Association, the American College of Obstetricians and Gynecologists, and others. In February 1980 the US District Court for the District of Delaware upheld FDA's authority to issue the estrogen PPI requirement under the drug misbranding section of the Federal Food, Drug, and Cosmetic Act. Among other things, the court also found that the requirement did not interfere with any constitutionally protected rights of physicians to practice medicine. This decision has recently been affirmed by the US Court of Appeals for the Third Circuit.

TABLE 1.—*Results of FDA Review of Patient Noncompliance Rates From Studies Completed After 1969*

Drugs	*No. of Studies*	*Percent Noncompliance*		
		Range	*Mean*	*Median*
Cardiac	3[1-3]	20-45	33	34
Antihypertensive	5[4-8]	24-83	43	33
Penicillin	8[9-16]	11-95	45	38
Other antibiotic	5[17-21]	37-71	52	50
Antituberculosis	4[22-25]	28-53	42	43
Antipsychotic	8[26-33]	19-63	42	48
Multiple drugs	11[34-44]	25-80	60	43
Miscellaneous	6[35-40]	28-89	52	49

Fallacy Number Three: Patients don't need such information. Unfortunately there is abundant evidence showing widespread failure by patients to use drugs properly. Patients most frequently misuse prescription drugs by failing to adhere to the prescribed regimen, such as improperly spacing doses, failing to take the drug for the time necessary for adequate treatment, skipping doses or taking extra doses. Researchers have estimated the extent of patient noncompliance at 30 percent to 80 percent. FDA's own patient prescription drug labeling project reviewed patient noncompliance rates from studies completed after 1969. Each study reviewed by FDA included at least 40 patients. The results of that review are presented in Table 1.

Fallacy Number Four: Patients don't want the information. Interest in patient labeling has been expressed most forcibly by consumer activists. But a number of surveys indicate that consumer advocates accurately reflect broad public support for patient labeling.

For example, a 1973 nationwide survey sponsored by FDA showed that 49 percent of the respondents wanted additional information in nontechnical language dispensed with the products.[41] Similar findings were made by independent researchers who found that of 828 students and outpatients studied, 82 percent wanted to know more about prescription drugs than simple direc-

tions for use, specifically information about side effects and risks from overuse or underuse of a prescribed drug.[42]

In 1975 FDA sponsored a nationwide survey of 1,720 users of orally taken contraceptives. They were asked if they would like to receive patient labeling with other prescription drug products. Of the respondents, 93 percent believed it to be important to provide patient labeling for antibiotics, and 97 percent believed it important for tranquilizers.[43]

Results of a 1978 survey supported these findings, with 64 percent of 2,002 adults surveyed stating that they believed it important for printed labeling to be provided with prescription drugs. Only 33 percent stated that current practices seemed adequate. This two-to-one preference for patient labeling was consistent across all age, sex and educational subgroups.[44]

In 1980 I took my own informal survey through a unique two-way television hookup in Columbus, Ohio, known as QUBE. Consumers who responded to a series of questions clearly supported more information about prescription drugs and indicated a willingness to pay for it.

Fallacy Number Five: FDA was "steamrolling" the PPI requirement through without adequate study, research or opportunity for criticism. FDA leaned over backwards to assure that adequate study was conducted and all concerned parties given an opportunity to voice opinions against as well as for the PPI program. Following the patient labeling requirement for oral contraceptives in 1970, FDA began evaluating the usefulness of patient labeling for prescription drug products generally and studied ways to present the information most effectively. In line with suggestions made by FDA's National Food and Drug Advisory Committee, FDA began a patient prescription drug labeling project in 1974 to investigate whether patient labeling efforts should be expanded to a variety of prescription drug products. After this project began, FDA discussed patient labeling issues with all interested and potentially affected persons and groups, reviewed scientific literature about the information needs of patients, carried out research projects to evaluate existing and model patient labeling, and reviewed existing methods for communicating drug information to patients.

For example, between September 1974 and June 1975, FDA officials met individually with nine organizations representing physicians, pharmacists and the pharmaceutical industry; and, in July 1975, officials met with consumer representatives to discuss the general concept of patient labeling. These meetings were highly productive, identifying such major concerns as the criteria for choosing candidates for patient labeling, the possibility that patient labeling would interfere in the patient/physician relationship, the problems patient labeling might pose to pharmacists, consumer support for patient labeling, liability issues, the problems of conveying patient information in nontechnical language, information that should be included in patient labeling, the need for physician discretion to withhold labeling in certain instances, and logistical problems that might be created by storage and distribution of the inserts.

After FDA was petitioned in 1975 by a consortium of consumer organizations that favored patient labeling, the agency published a notice in the *Federal Register* soliciting comment. FDA received more than a thousand comments in response to this notice, all of which were carefully evaluated. In May and June 1976 FDA hosted four meetings at which consumer advocates and FDA officials met with representatives from the pharmaceutical industry, medical and pharmacy associations, and allied health professions to debate the issues raised by the consumer petition.

In 1976 FDA also invited the Drug Information Association, an independent nonprofit professional group interested in drug information, to arrange a symposium on patient labeling for prescription drug products at which a diversity of views could be presented. This symposium, held in November of 1976, was also cosponsored by the American Medical Association and the Pharmaceutical Manufacturers Association. More than 700 health professionals, consumers and information media representatives attended the symposium, the proceedings of which were published in January 1977 as a special supplement to Volume II of the *Drug Information Journal.*

FDA continued to solicit public comment on patient labeling, as exemplified by its having sponsored a two-day conference on the content and format of patient labeling. In February 1979, the Institute of Medicine of the National Academy of Sciences, under contract to FDA, sponsored a public hearing to solicit comments on how patient labeling should be objectively evaluated, once it is used on a widespread basis.

In addition, to stimulate comment on the proposal to require PPI's for certain drugs, FDA an-

nounced in August 1979 that three public hearings on the proposal would be held—in Chicago, Los Angeles and Washington, DC, respectively, on September 10, 12 and 14, 1979. The agency received some 1,500 comments from trade associations and individual firms involved in the manufacture and distribution of prescription drug products; from organizations of health care professionals and individual physicians, pharmacists, and members of other health care professions; from organized consumer groups and individual consumers, and from others.

A summary of the substantive comments on the proposal and FDA's responses appear in the preamble to the regulation published on September 12, 1980. A transcript of the public hearings is available for study in the FDA Hearing Clerk's office.

Finally, what FDA established in the PPI regulations it issued in September 1980 is a three-year pilot program for PPI's to be used to evaluate all the issues surrounding PPI's—including content, format, method of distribution and effectiveness—based on the experience gained with the ten drugs or drug classes for which PPI's would be required. In sum, I can think of no other FDA activity that has been more thoroughly studied than PPI's.

Fallacy Number Six: Patient labeling would have a detrimental psychological effect on patients. This is a concern that FDA has taken quite seriously. The agency has studied the literature on the effects of written information and found that it does not sustain this objection to patient labeling. Studies that have examined the rate of patient-reported side effects have found no difference between patients who received written information and patients who did not. One study did show that patients who received information were more willing to *report* side effects than patients who did not receive this information.[48]

In addition, an FDA-sponsored study evaluated the effect of a patient labeling piece for the antihypertensive thiazide drugs.[49] The study involved 249 patients in whom mild essential hypertension had been newly diagnosed. Two thirds of the patients were assigned randomly to a group that received the patient labeling. The remainder were assigned to a group that did not receive it. Preliminary results do not suggest an increased incidence of adverse effects in the patients who received the labeling. They were, however, better informed about the drug product and less likely to attribute physical complaints to it.

Accordingly, current studies do not support the contention that patient labeling will have negative effects on patients' use of prescription drug products. As part of the pilot program, FDA would continue to gather and review data on the effects of patient labeling on prescription drug use and would, of course, take into account any new information or insights in developing its patient labeling program.

In those instances where the physician believes that a patient package insert should not be given to the patient, the regulation would permit the dispenser to withhold the insert except for certain enumerated drugs, such as estrogen, and where patients specifically request the insert.

Fallacy Number Seven: Patient labeling would reduce a drug's placebo effect. The placebo effect is, of course, complicated and poorly understood. Much of the effect appears to be due to the relationship between physician and patient. Because the patient receiving a PPI would possess more knowledge about what effects to expect from a particular drug, and because patient labeling may enhance patient-physician communications, information in PPI's about the effects of the drug may even increase the placebo effect of the drug product.

Fallacy Number Eight: PPI's would merely add to the counseling burden of physicians forced to reassure frightened patients. It was expected that in most cases the information conveyed in the PPI would merely restate and reemphasize the information that the physician has given the patient when the product was prescribed. In such a case, it should not alarm a patient any more than did the oral information, nor should it significantly increase the length or number of contacts between physicians and patients. Further, patient labeling might help patients ask clearer questions than they now ask, thereby aiding the physician to come more rapidly to a precise response. This is confirmed by an FDA survey that showed only 12 percent of oral contraceptives users who said they read the labeling also said that it raised questions that caused them to contact their physicians.[43] Many of these questions were related to effects not mentioned in the labeling but experienced by the patients, such as spotting, bleeding, breast soreness and weight gain. Moreover, added patient-physician contact is not necessarily an untoward result of patient labeling. It is quite likely to lead to a patient population that is better educated about drug therapy and, thus, more likely to

comply with physicans' drug therapy efforts. It seems logical that less complete information would lead to greater need to contact physicians than more complete information.

Fallacy Number Nine: A survey showed that people exposed to PPI's actually know less than those who are not exposed to them. There is no such survey. This misconception may have arisen from another, quite different survey, showing that people exposed to PPI's *plus* counseling knew more than people exposed to PPI's alone, a result we would certainly expect.

Fallacy Number Ten: PPI's would be required for all drugs. The regulation announced in September 1980 involved ten drugs or categories of drugs: the ampicillins, benzodiazepines, cimetidine, clofibrate, digoxin, methoxsalen, phenytoin, propoxyphene, thiazides and bendectin (which was recently substituted for one of the original ten, warfarin).

In selecting these drugs, FDA considered the following factors: whether precise use of the drug is essential in achieving its therapeutic effect, whether the drug is widely prescribed and used, whether the drug has the potential of causing significant adverse effects, whether there are likely to be severe problems if patients do not follow the dosage schedule and directions for use, and whether use of the drug is largely a matter of personal choice by patients.

Fallacy Number Eleven: Physicians would be unable to prescribe a drug for an indication not contained in the PPI. FDA recognized that prescription drug labeling, including both professional and patient package inserts, does not always contain the most current information available to practitioners about the proper use of a drug. Because advances in medical knowledge and practice inevitably precede formal changes in prescription drug labeling, good medical practice and patient welfare *require* that practitioners remain free to use prescription drugs according to their best knowledge and judgment. Nothing in the Federal Food, Drug and Cosmetic Act prohibits practitioners from prescribing a drug product for a particular patient for an indication not contained in its labeling, and the PPI regulation does not change this general rule. Moreover, the patient package insert required under the regulation might not need to identify all indications for which a drug product is legally marketed. The agency intends to include in some of its guideline patient package insert texts the following statement which would deal effectively with this issue: "This drug may be used for other conditions as determined by your doctor."

Fallacy Number Twelve: PPI's are a vehicle whereby the government could impose its views of proper drug prescribing practices. PPI's are no more such a vehicle than are professional package inserts, almost all of which are approved by FDA before they are put into use. Moreover, although FDA would prepare and provide guideline patient package inserts that manufacturers, distributors, and dispensers could use to comply with the regulations, those persons would be free to prepare their own patient package inserts in compliance with the regulations.

Fallacy Number Thirteen: The PPI Program was mandated regardless of consequences. The PPI program was consistent with recommendations made in August 1979 by the Institute of Medicine of the National Academy of Sciences. The Institute of Medicine called for a comprehensive study of patient package inserts, pointing out that experience with inserts has been positive and that the most pressing need is for more research and testing of PPI systems in actual use. As a consequence, the regulations for the ten PPI's were cast in terms of a pilot project for a three-year evaluation period during which FDA would study the actual costs, benefits and other effects of patient package inserts, as well as alternative patient information systems.

Fallacy Number Fourteen: The PPI program sought to alter, or would alter, the traditional patient-physician relationship. PPI's would not adversely affect the roles played by physicians, or pharmacists, in patient care. The purpose is not to interfere with physicians but rather to see to it that information is made available that a patient can use to carry out a physician's directions, information that many believe would help transform the position of a great number of patients from passive compliance to active cooperation with physicians in a prescribed course of therapy.

I hope my discussion of these 14 "fallacies" has helped bring the proposed FDA PPI program into better focus. It is not surprising that so many questions arose about a program that would directly affect as many patients and health professionals as the PPI program would.

Addendum

As this article goes to press, the Reagan Administration is preparing to go to the *Federal*

Register with an indefinite stay of the patient labeling regulations. It is their intent to reconsider the proposal and the final outcome is thus in some doubt. I continue to believe in the approach we developed, which would generate some answers as to the best way of educating patients about prescription drugs, and hope the new administration decides to continue the experiment.

REFERENCES

1. Spector R, McGrath P, Uretsky N, et al: Does intervention by a nurse improve medication compliance? Arch Intern Med 138: 36-40, 1978

2. Weintraub M, Au WYW, Lasagna L: Compliance as a determinant of serum digoxin concentration. JAMA 224:481-485, 1973

3. Marsh W, Periman L: Understanding congestive heart failure and self-administration of digoxin. Geriatrics, Jul 1972, pp 65-70

4. Abernethy JD: The problem of non-compliance in long-term antihypertensive therapy. Drugs 11(Suppl 1):86-90, 1976

5. Eshelman FN, Fitzloff J: Effect of packaging on patient compliance with antihypertensive medication. Curr Ther Res 20: 215-219, 1976

6. Fletcher S, Appel FA, Bourgeois MA: Management of hypertension—Effect of improving patient compliance for follow-up care. JAMA 233:242-244, 1975

7. Sackett DL, Haynes RB, Gibson ES, et al: Randomized clinical trial of strategies for improving medication compliance in primary hypertension. Lancet 1:1205-1207, May 31, 1975

8. McKenney J, Slining JM, Henderson HR, et al: The effect of clinical pharmacy services on patients with essential hypertension. Circulation 48:1104-1111, 1973

9. Leistyna J, Macaulay J: Therapy of streptococcal infections. Am J Dis Child 3:22-26, 1966

10. Gordis L, Markowitz M, Lilienfeld AM: The inaccuracy of using interviews to estimate patient reliability in taking medications at home. Med Care 7:49-54, 1969

11. Gordis L, Markowitz M, Lilienfeld AM: Why patients don't follow medical advice: A study of children on long-term antistreptococcal prophylaxis. J Pediatr 75:957-968, Dec 1969

12. Gordis L, Markowitz M: Evaluation of effectiveness of comprehensive and continuous pediatric care. Pediatrics 48:766-776, 1971

13. Colcher IS, Bass JW: Penicillin treatment of streptococcal pharyngitis. JAMA 222:657-659, Nov 6, 1972

14. Charney E, Bynum R, Eldredge D, et al: How well do patients take oral penicillin: A collaborative study in private practice. Pediatrics 40:188-195, 1967

15. Gordis L, Markowitz M, Lilienfeld AM: Studies in the epidemiology and preventability of rheumatic fever. Pediatrics 43:178-182, 1969

16. Mattar M, Markello J, Yaffe SJ: Pharmaceutic factors affecting pediatric compliance. Pediatrics 55:101-108, 1975

17. Sharpe T, Mikeal R: Patient compliance with antibiotic regimens. Am J Hosp Pharm 31:479-484, 1974

18. Becker M, Drachman RH, Kirscht JP: Motivations as predictors of health behavior. Health Service Rep 87:852-862, Nov 1972

19. Meyers A, Dolan T, Mueller D: Compliance and self-medication in cystic fibrosis. Am J Dis Child 129:1011-1013, 1975

20. Arnhold RG, Adebonojo FO, Callas ER, et al: Patients and prescriptions: Comprehension and compliance with medical instructions in a suburban pediatric practice. Clin Pediatr(Phila) 9:648-651, 1970

21. Bergman A, Werner R: Failure of children to receive penicillin by mouth. N Engl J Med 268:1334-1338, 1963

22. Preston D, Miller F: The tuberculosis outpatient's defection from therapy. Am J Med Sci 247:21-24, 1964

23. Onstad D, Sharbaro JA, Rotenberg L: Posthospital chemotherapy of the unreliable patient. Am Rev Respir Dis 101:258-264, 1970

24. McInnis J: Do patients take antituberculosis drugs? Am J Nurs 70:2152-2153, 1970

25. Hecht A: Improving medication compliance by teaching outpatients. Nurs Forum 13:112-129, 1974

26. Ballinger B, Ramsay AC, Stewart MJ: Methods of assessment of drug administration in a psychiatric hospital. Br J Psychiatry 127:494-498, 1975

27. Rickels K, Raab E, Gordon PE, et al: Differential effects of chlordiazepoxide and fluphenazine in two anxious patient populations. Pyschopharmacologia 12:181-192, 1968

28. Johnson DAW, Freeman H: Long-acting tranquilizers. Practitioner 208:395-400, 1972

29. Parkes M, Brown GW, Monck EM: The general practitioner and the schizophrenic patient. Br Med J 1:972-975, Apr 7, 1962

30. Hare EH, Willcox DRC: Do psychiatric in-patients take their pills? Br J Psychiatry 113:1435-1439, 1967

31. Baekeland F, Lundwall L: Effect of discontinuity of medication on the results of a double-blind drug study in outpatient alcoholics. J Stud Alcohol 36:1268-1271, 1975

32. Willcox DRC, Gillan R, Hare EH: Do psychiatric outpatients take their drugs? Br Med J 2:790-792, 1965

33. Irwin D, Weitzel WD, Morgan DW: Phenothiazine intake and staff attitudes. Am J Psychiatry 127:67-71, 1971

34. Rickels K, Briscoe E: Assessment of dosage deviation in outpatient drug research. J Clin Pharmacol 10:153-160, 1970

35. Porter AMW: Drug defaulting in a general practice. Br Med J 1:218-222, 1969

36. McKenney J, Harrison W: Drug-related hospital admissions. Am J Hosp Pharm 33:792-795, 1976

37. Brand F, Smith RT, Brand PA: Effect of economic barriers to medical care on patients' noncompliance. Public Health Rep 92:72-78, 1977

38. Mushlin A, Appel F: Diagnosing potential noncompliance. Arch Intern Med 137:318-321, 1977

39. Latiolais C, Berry C: Misuse of prescription medications by outpatients. Drug Intelligence Clin Pharm 3:270-277, 1969

40. Miller W: Drug usage: Compliance of patients with instructions on medication. J Am Optom Assoc 75:401-404, 1975

41. Knapp DE: Consumers and Medication, FDA Report No. FDA-D-ADMC-4. Springfield, VA, National Technical Information Service, 1974

42. Fleckenstein L, Jaubert P, Lawrence R, et al: Oral contraceptive patient information: Questionnaire study of attitudes, knowledge, and preferred information sources. JAMA 235:1331-1338, 1976

43. Morris LA, Mazis M, Gordon E: A survey of the effects of oral contraceptive patient information. JAMA 238:2504-2508, 1977

44. Mazis M, Morris L, Gordon E: Patient attitudes about two forms of oral contraceptive information. Med Care 16:1045-1054, 1978

45. Eklund LB, Wessling A: Evaluation of package enclosures for drug packages. Lakartidningen 73:2319-2320, 1976 (Swedish)

46. Bass M, Suveges L: The impact of counseling by the pharmacist on patient knowledge and compliance. Research paper under direction of Martin Bass, University of Western Ontario, Canada, 1977

47. Weibert R: Patient package inserts: Potential distribution problems. Drug Inform J 11:458-498, 1977

48. Paulson P, Bauch R, Paulson MJ, et al: Medication data sheets—An aid to patient education. Drug Intelligence Clin Pharm 10:448-453, 1976

49. Kanouse DE, Morris LA: Patient package inserts: Effects on patient knowledge, attitudes and behavior. Presented at American Public Health Association meeting, October 1978, Los Angeles

IDAHO MEDICAL ASSOCIATION

89th Annual Meeting

July 22-25, 1981 • Sun Valley, Idaho

AN INVITATION TO SUN VALLEY July 22-25, 1981

An outstanding scientific medical program and beautiful gr
Sun Valley. This is a combination treat that should tempt
physicians to attend our 89th Annual Meeting of the Idaho M
ical Association. Nine credit hours of Category 1 are availal

Attractive social activities for the members of the medical far
are available, with golf, a tennis tournament, swimming, cycli
horseback riding, bowling, fishing, trapshooting and much m
We do hope that you will join us.

W. Dyce Thurston,
President
Idaho Medical Associati

89th Annual Meeting
Idaho Medical Association
Sun Valley—July 22-25, 1981

SUN VALLEY REGISTRATION FORM

Name _____

Address _____

City _____ State _____ Zip _____

Will Arrive _____, 1981 at _____ &

Depart _____, 1981 at _____.

Confirmed reservations require an advance deposit equal to one night's room rental. PLEASE RETURN FORM WITH DEPOSIT TO:

SUN VALLEY RESERVATION OFFICE
SUN VALLEY, IDAHO 83353

Questions? Call Sun Valley Toll-free reservations number (800) 635-8261.
Please mention IMA meeting when calling Sun Valley.

Please Check Accommodations Desired*

At the
LODGE, INN or LODGE APARTMENT ROOM

- ☐ Single, $48 per day
- ☐ Double, $54 per day

At the
LODGE APARTMENT SUITES or CONDOMINIU

- ☐ Studio, $53 per day
- ☐ One-Bedroom, $88 to $98 per day
- ☐ Two-Bedroom, $127 to $149 per day
- ☐ Three-Bedroom, $159 to $193 per day

Deadline for Reservations—June 22, 1981

Deposit forfeited for cancellation received than 7 days prior to arrival; $10 per person p essing charge on all cancellations.

*European Plan

IDAHO MEDICAL ASSOCIATION

89th Annual Meeting

JULY 22-25, 1981

WEDNESDAY

8:30 am-
5:00 pm HOUSE OF DELEGATES

THURSDAY

MANAGEMENT OF STRESS

8:15 am Introduction
Theodore A. Walters, MD, Chairman
IMA Program Committee

8:30 am Physicians' Personality & Environment, or How We Got That Way
Beverley T. Mead, MD

9:30 am Physiological Effects of Stress
Margaret Chesney, PhD

1:00 am Families Under Stress
Sharon Wegscheider

1:30 pm Stress-Related Behavior: Alcohol and Drugs
Joseph A. Pursch, MD

2:30 pm Identifying Family Roles and Behavior/
What To Do If It Doesn't Work
Sharon Wegscheider

4:00 pm Therapy of Drug Dependence
Joseph A. Pursch, MD

5:00 pm Adjournment

FRIDAY

8:15 am Introduction
Theodore A. Walters, MD

8:30 am Changing Type A Behavior
Margaret Chesney, PhD

9:30 am Avoiding the Pitfalls/Making the Future More Satisfying
Beverley T. Mead, MD

11:00 am Panel Discussion: (Written and Verbal Questions from Audience)
Margaret Chesney, PhD **Joseph A. Pursch, MD**
Beverley T. Mead, MD **Sharon Wegscheider**

12 noon Adjournment

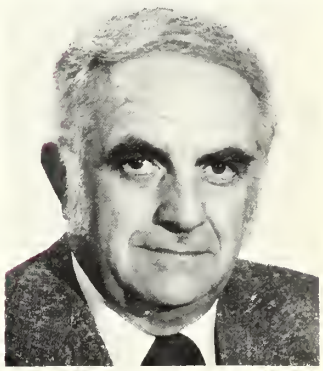
SATURDAY

8:30 am Closing Session, House of Delegates

REGISTRATION FEE $125 FOR NON-IMA MEMBERS AND OUT-OF-STATE PHYSICIANS.

For information contact:
IDAHO MEDICAL ASSOCIATION
P.O. BOX 2668
BOISE, IDAHO 83701 TELEPHONE: (208) 344-7888

Margaret Chesney, PhD
Director and Senior Health Psychologist
Behavioral Medicine Program
Stanford Research Institute



Beverley T. Mead, MD
Associate Dean and Professor of Psychiatry, Creighton University School of Medicine, Omaha

Joseph A. Pursch, MD
Corporate Medical Director
CareManor Hospital, Orange, CA
Special Assistant to the Navy Surgeon General on Alcoholism

Sharon Wegscheider
President
Onsite Training and Consulting, Inc.
Minneapolis

BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

RESPIRATORY PHYSIOLOGY—Ths Essentials—Second Edition—John B. West, MD, PhD, Professor of Medicine and Bioengineering, University of California, San Diego, School of Medicine, La Jolla The Willams & Wilkins Company, 428 E. Preston St., Baltimore (21202), 1979. 182 pages, $11.50 (paperback).

This second edition paperback is described by the author as being "primarily written as a core course for medical students." With this intent, the author has succeeded in developing a clear and fundamental description of lung physiology. In this regard physicians as well as students will benefit from the author's concise approach. In particular he has carefully chosen effective figures to complement his text. A collection of these figures, in fact, could be put to good use by others who teach pulmonary physiology. In the preface, the author describes the changes from his first edition. He has made key improvements, most notably decreasing the section on ventilation-perfusion relationships. This undoubtedly took restraint, as this is his key field of research interest. Although his section on metabolic functions of the lung has grown, it is still too brief. This relates to the author's admission that his bias is that the "chief business of the lung is gas exchange." Furthermore, this book with its deserved wide appeal to medical students should include a section on the lung's defense system. Interest in environmental and occupational lung disease is burgeoning. A rudimentary section on defense mechanisms is certainly appropriate in this context.

The book begins with basic lung anatomy. The electron micrographs are particularly effective in giving a visual representation of the lung structure and function relationship. Next, his discussion of ventilation includes the basis of ascertaining lung volumes in the pulmonary function laboratory. He describes the two basic methods, gas dilution and body plethysmography. He gives a short description of regional differences in ventilation which is a very useful clinical topic, especially in the intensive care unit setting. His review of diffusion is good. It lacks specific references as to the role of abnormal diffusion as a cause of hypoxia, the "capillary-block controversy." He does make general statements on this issue, however. His discussion of pulmonary blood flow is excellent. He again stresses regional differences which are so clinically important today with the use of PEEP (positive end-expiratory pressure), pulmonary arterial catheters and the like. His review of ventilation-perfusion relationships is the best chapter in the book. This is an area in which the author draws upon his own background both as a researcher and a teacher. It is an area of tremendous clinical interest in terms of abnormal gas exchange. He deals with the mechanics of breathing in a way that clarifies the clinical significance of our newest laboratory techniques: airway resistance, maximal expiratory flow volume curves using air and helium-oxygen-gas mixtures, closing volumes and so forth. His rewritten chapter on control of ventilation is clear. Given his didactic objectives, he carefully avoids confusing detail in this very confusing area of pulmonary physiology.

The chapter on unusual environments is fascinating, especially given the prior review of physiology. However, four paragraphs on polluted atmosphere is too short, especially given the author's comments that "a polluted atmosphere is becoming less and less of an unusual environment." Finally, his chapter on pulmonary function tests is very effective, especially given the physiologic background in the previous chapters. One criticism, however, is that exercise physiology testing is given only five sentences. The author's clear style should have been applied to exercise physiology as well. It is an area that will become more and more important in medicine of the 1980's.

This book accomplishes its stated objectives. It is a lucid and logical description of pulmonary physiology. Anyone who wants to review pulmonary physiology especially as it relates to clinical medicine should read this book.

JEFFREY A. GOLDEN, MD
Assistant Clinical Professor
Department of Medicine
University of California, San Francisco

* * *

THE HUMAN PATIENT—Naomi Remen, MD. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1980. 238 pages, $10.95.

It is not often that one has the privilege of reviewing a book that is destined to become a classic in medicine. *The Human Patient* is such a book. In the freshness of its insight and the practicality of its discussion, it most resembles another classic, *The Doctor, His Patient and the Illness* by Michael Balint, which also reviewed the scope of relationships between health professional and patient/client in a way that expanded the understanding of both parties in this complex relationship. It surpasses Dr. Balint's book in that it manages, amazingly, to speak equally well to both health professionals and patients. It seems to do this by being able to address the human being present in each health professional and the healer present in each patient.

In the introduction, entitled "Science and Human Needs," Dr. Remen states the premise, perhaps the hope, that it is possible for us to take advantage of the benefits of science and technology without sacrificing our human values in the process. The chapter entitled "What's Right With the Patient" illustrates how even in illness, the strengths of individual persons can be supported and discusses the limits and risks of diagnostic labeling. Subsequent chapters practically illustrate how these strengths can be mobilized. Particularly useful is the chapter on "A Healthy Way to Have a Disease," which guides both professional and patient into obtaining the full personal growth and value from an illness experience in a way which supports appropriate medical treatment *and* the life values of the person and families involved.

The myth that humanistically oriented care is too time consuming to ever be practical is carefully dispelled in the chapter on "Clock Time and Life Time." The final chapters on "Free Choice" and "Collaborative Caring" outline the genuine degrees of freedom for both health professional and patient even with the constraints of serious illness and limited family resources.

Dr. Remen draws richly on her experiences as a practicing clinician and an academician experienced in health professional education, as a founding member of the Institute for Humanistic Medicine and in the Collaborative Health Project, which has brought together physicians, nurses and consumers in an effort to identify strategies that mutually support all parties in health care.

The book addresses the broader conceptual issues in

simple but not simplistic language. The points are amply illustrated by case studies drawn from actual practice, which allow readers to relate the discussions to their own experiences, either as care giver or receiver. I feel the book should be required reading for all health professionals in training, indeed for all of us as patients-to-be. *The Human Patient* does not shout or preach, but speaks softly and clearly to the best in all of us.

DONALD L. FINK, MD
Professor of Family and Community Medicine
University of California
San Francisco School of Medicine
San Francisco

* * *

THE COURAGE TO FAIL—A Social View of Organ Transplants and Dialysis—Second Edition, Revised—Renée C. Fox, Professor, Departments of Sociology, Psychiatry and Medicine, and Annenberg Professor of the Social Sciences, University of Pennsylvania; and Judith P. Swazey, Professor, Socio-Medical Sciences Department, Boston University School of Medicine, and in Department of History, Boston University, and member of Special Scientific Staff (Pediatrics) at Boston City Hospital. The University of Chicago Press, 5801 E. Ellis Ave., Chicago (60637), 1978. 437 pages, $6.95 (Paperback).

We reviewed the first edition of this book in 1975 and noted that it sounded an alarm to all in the health care system. We were enthusiastic about it and recommended that all health care participants read it: physicians, their extenders, policy makers, and patients and their families. Not only was the style concise and readable, but the overview it presented of the field of organ transplantation and dialysis was thorough and comprehensive. In particular it spotlighted the growing moral, ethical, economic and clinical problems that are part of this large social experiment, as a consequence of Public Law 92-603 which supported renal dialysis and kidney transplantation. This was the first social commitment to support fully the clinical care and life needs of a single chronic illness (end-stage uremia).

Renée Fox and Judith Swazey set forth their account in a journalistic rather than a scientific fashion, but this should not deter the thoughtful reader for here in one comprehensive and highly readable book are portrayed all the characters and events of this frontier field set in the framework of technical achievement and social conscience. The contents, for instance, include a broad panoramic overview of the dialysis and transplant innovations and a conceptualization of the "courage to fail ethos"; and intimate, almost eavesdropping, evaluations and interviews with and of the scientific innovators themselves: Barnard, Cooley, DeBakey in the heart transplant field, and the poignant, views of Scribner whose pioneering work with renal dialysis and the invention of the plastic cannula which made it all possible.

To dramatize how these issues impinge upon actual cases, the authors focus on two in particular: that of the artificial heart and that of Ernie Crowfeather. In the first case, that of the artificial heart, a Mr. Karp received a mechanical heart and after his death, Mrs. Karp alleged negligence and claimed the lack of informed consent and the presence of improper experimental controls (the mechanical device had not received sufficient clinical trials in animals). The entire court procedures are included, as well as intimate interviews with the "pump team."

The second case is that of Ernie Crowfeather. He was an American Indian by ancestry though not by personal identity, who lost his first kidney following a bicycle accident. The remaining kidney later became infected and he moved inevitably into the health delivery system where for the next thirty months, at the cost of an estimated $100,000, his life was prolonged. He cared little for himself, never followed the therapeutic regimen and even while rejecting his kidney, was in and out of jail. Finally he died alone in a motel (suicide), even while his doctors rushed there to save him. One physician asked the anguishing question "What was the meaning of his life?"

This second edition is literally reprinted from the plates of the first but it omits one chapter (on the social portrait of a transplant surgeon misinterpreted by critics as a eulogy) and adds three new ones which report on the changing perspectives in renal dialysis and organ transplantation. Here the clinical outcome of transplantation is documented with a state-of-the-art review of the major programs in organ transplantation: heart, liver, kidney, bone marrow (lung and pancreas are not covered). In all of these fields they find less clinical audacity evident (replaced by increasing humility) for there has been no fundamental progress in the past ten years in understanding or managing the immunological problems related to rejection.

In the renal dialysis program, however, activity during the past ten years has been a different story altogether. Here the authors point out the enormous increase in the number of "proprietary" centers in this field (with the National Medical Care Organization [listed on the New York Stock Exchange] as a vivid example), and review the debate over costs (including comparisons between home and center based dialysis). In particular they are concerned over the change in overall policy that this program represents, and the implications it may have for the future of medicine. With the passage of PL 92-603, they point out, this particular form of treatment has been "democratized." No longer is the physician the "gatekeeper," or clinical policy the criterion for patient selection. If the therapy is paid for and available to all, it is perceived as immoral not to offer it to anyone who desires it. Furthermore, this legislative approach reinforces the illusion that technical intervention will somehow cure the disease or improve the quality of life of the recipient.

Throughout the book the sensitive reader experiences a constant anguishing identification with the chronically ill candidate for one of these life-prolonging therapies. One begins to appreciate the nature of human helplessness in all its facets: the inability to control the course of the disease as it moves ineluctably toward death, the increasingly limited options to negotiate for one's personal and social needs within the health care system, the loss of dignity as an experimental subject, or (worse) as a commodity in an entrepreneurial system.

In conclusion the authors question (page 344) whether it might be "helpful or harmful to make all those who participate in clinical research more aware of the therapeutic innovative process with all its intended and unintended consequences," and suggest that such a move might . . . "permit them to guide and alter the process in ways that would mitigate the suffering of the 'black years'; reduce the possibility that episodes like the heart transplant 'bandwagon' will occur; make physicians less medically and morally reluctant to call moratoriums on their own clinical trials; lead to different stages of the therapeutic process; make it less probable that physicians' biomedical reasoning about patient selection will be so directly and significantly affected by changes in the political economy of health care delivery; and make it more likely that the psychological, social and cultural aspects of the process will be handled with greater insight and deliberation?" We think so, and we believe that

these developments would render the process of therapeutic innovation more rational, flexible, governable, biomedically fruitful, ethical and humane.

The march of science ever creating the possibility of innovative technologies to alter disease continues to nudge against the existing social norms of ethics, morality, economics, law and politics demanding change. We are now in the center of a large, yet unevaluated, social experiment, the consequence of PL 92-603. What seems to be emerging among other things, is the conclusion that physicians may participate less and less in health care decisions. Furthermore, the question of "worth" both to the individual person and society needs to be evaluated with health care innovative technologies, before their release for general use. In conclusion, the book does sound an alarm. It cries out for medical leadership, not a defense of the system. We reiterate, that all in the health care system should study it for the medical models presented.

H. HARRISON SADLER, MD
Clinical Professor, Psychiatry and Ambulatory Medicine
Associate Dean
School of Medicine
University of California, San Francisco

* * *

HANDBOOK OF OBSTETRICS & GYNECOLOGY—Seventh Edition— Ralph C. Benson, MD, Clinical Professor of Obstetrics and Gynecology and Emeritus Chairman, Department of Obstetrics and Gynecology, University of Oregon Health Sciences Center, Portland. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1980. 808 pages, $10.00.

As always, a useful student guide to be used in the obstetric-gynecology clerkship.

MORTON A. STENCHEVER, MD
Professor and Chairman
Department of Obstetrics and Gynecology
University of Washington School of Medicine
Seattle

* * *

ANNUAL REVIEW OF NEUROSCIENCE—Volume 3, 1980—Editor: W. Maxwell Cowan, Washington University School of Medicine; Associate Editors: Zach W. Hall, University of California, San Francisco; and Eric R. Kandel, College of Physicians and Surgeons of Columbia University. Annual Reviews, Inc., 4139 El Camino Way, Palo Alto, CA (94306), 1980. 428 pages, $17.00.

As its title indicates, this is the third volume of reviews of the rapidly expanding field of neurobiology which is the science basic to the medical fields of neurology, neurosurgery, psychiatry and anesthesiology. There are 14 reviews written by outstanding scientists in the field. The range of topics covered largely reflects the interests of basic scientists with a smattering of clinically oriented material. This particular volume is heavily weighted toward neurogenesis. Of the 14 reviews, 6 deal with problems related to the development of the nervous system. The general problem is one of defining what factors determine the specificity of connections and what stimulates outgrowth of nerve processes. The promise and limitations of various approaches are clearly outlined. The problem for the general reader is succinctly stated by Fraser and Hunt, page 330, ". . . as the experiments have become more complex the results have become more kaleidoscopic." Fraser and Hunt review studies on regeneration by retinotectal connections in amphibia.

Greene and Shooter discuss the properties of nerve growth factor, a polypeptide that may be necessary for growth and survival of certain types of neurons. Other reviews of development, specificity and cell-cell recognition were contributed by Victor Hamburger, Lynn Landmesser, Gottlieb and Glazer and Anderson, Edwards and Palka. The review by Baldessarini and Tarsy on drug-induced dyskinesias is a concise and readable discussion of the evidence that antipsychotic drugs act on a dopamine receptor in the central nervous system to produce their extrapyramidal side effects. Therapy for these conditions is also reviewed. Terry and Davies update us on research in Alzheimer disease (senile dementia). Although most studies are detailed descriptions of the pathological features, new approaches are being taken. One intriguing finding is a drop in the activity of an enzyme involved in acetylcholine synthesis.

In addition to the above, the review by Jonsson of neurotoxins specific for certain types of nerve cells and the discussion by Nicole and co-workers on substance P will attract the interest of a broad range of neuroscientists.

In summary, this set of reviews is aimed primarily at neuroscientists. The reviews on Alzheimer and drug-induced extrapyramidal syndromes will be of interest to neuroclinicians. Academicians in brain-related clinical fields will also find much of value in the other reviews. The quality of the reviews is consistently high, reflecting the outstanding caliber of the contributors. At $17 this book is quite a bargain.

HOWARD L. FIELDS, MD, PhD
Associate Professor of Neurology and Physiology
University of California, San Francisco

* * *

PRACTICAL RHEUMATOLOGY: DIAGNOSIS AND MANAGEMENT— Rodney Bluestone, MB, FRCP, Clinical Professor of Medicine, University of California, Los Angeles; Associate Attending Physician, Cedars-Sinai Medical Center, Los Angeles. Addison-Wesley Publishing Company, Inc., Health Sciences Division, 2727 Sand Hill Road, Menlo Park, CA (94025), 1980. 239 pages, $23.95.

The objective of this book is to provide a concise and practical clinical approach to the care, both in terms of diagnosis and therapy, of patients presenting with musculoskeletal symptoms. The book is divided into two parts and contains 12 chapters.

Part One is concerned with diagnosis and contains brief but very practical chapters discussing the target organs (such as joints and periarticular tissues), diagnostic value of the classic symptoms and signs of musculoskeletal diseases, physical examination of joints, radiographic survey for articular disease, and how to use the more common and important laboratory tests.

Part Two, entitled "The Clinical Profiles," contains individual chapters detailing various clinical aspects of broad catagories of musculoskeletal disease arbitrarily categorized for the purpose of this book. They include soft tissue rheumatism and other ill-defined syndromes, osteoarthrosis, chronic nonspecific inflammatory arthritis (for example, rheumatoid arthritis), chronic nonspecific inflammatory spondyloarthropathies, acute monarticular arthritis and collagen-vascular diseases.

All of the chapters were written by Dr. Rodney Bluestone, a well-known and respected clinical rheumatologist. The book is generally well illustrated and each chapter contains a modest number of suggested readings, most often standard texts. General approaches are stressed allowing recognition of particular problems, and accepted methods of treatment are discussed. The chapters on detection of articular signs, soft tissue rheumatism and rheumatoid arthritis are particularly useful. I commend the author for listing the various materials for patient education, especially those from the Arthritis Foundation. Many primary care physicians may not even be aware that these excellent materials exist.

There are no glaring weaknesses in the book, realizing

what the objectives are. It might have been valuable, however, to have stressed the importance of bacteriologic examination of synovial fluid removed at the time of intraarticular corticosteroid therapy in patients with rheumatoid arthritis in whom there are one or two joints with inflammation out of proportion to other involved joints.

As an introduction to the general approaches to diagnosis and treatment of musculoskeletal disorders, this book should be useful and interesting for general and primary care internal medicine physicians, medical and family practice residents, medical students and primary care nurses.

DICK L. ROBBINS, MD

Assistant Professor of Medicine
Section of Rheumatology
Department of Internal Medicine
School of Medicine
University of California, Davis

* * *

TO MAKE THE PATIENT READY FOR ANESTHESIA: MEDICAL CARE OF THE SURGICAL PATIENT—Edited by Leroy D. Vandam, MD, Peter Bent Brigham Hospital and Harvard Medical School, Boston. Addison-Wesley Publishing Company, Inc., Health Sciences Div., 2727 Sand Hill Road, Menlo Park, CA (94025), 1980. 245 pages, $24.95.

In this attractive handbook outlining the medical preparation of adult and especially geriatric patients for anesthesia and surgical procedures, Dr. Vandam and his 16 Peter Bent Brigham Hospital contributors (consultants) have provided busy anesthesiologists, surgeons, family practitioners and internists with a capsulized up-to-date guide for better understanding and treating the complex diseases which they confront daily in preparing their patients for anesthesia and operations.

In the chapter on the heart and circulation Drs. Goldman and Wolf review the cardiovascular response to anesthesia and surgical procedures, give guidelines for estimating perioperative cardiovascular risk, list essentials for a preoperative evaluation, and suggest procedures or drugs to enhance the perioperative and postoperative periods. Their conclusion is reassuring: "Despite the prevalence of underlying heart disease in American adults, indicated surgical procedures can usually be performed with an acceptable risk of cardiac-related mortality."

Drs. Hensley and Fencl in the chapter on lungs and respiration introduce the subject by reviewing the effect of general anesthesia for operations on respiratory function. They then go on to cover several respiratory disorders without undue emphasis on abstruse formulae and measurements. Finally some common sense guidelines for preoperative assessment and management are offered the reader.

Dr. LaMont provides a fascinating chapter on anesthesia and surgical procedures for patients with liver disease. He stresses (1) preoperative evaluation of liver function tests, (2) the possible deleterious effects of anesthesia and operation in the patient with liver disease, (3) the pathophysiology and clinical features of postoperative jaundice—including "halothane hepatitis."

In the large chapter on the renal system Drs. Narins and Lazarus offer advice on (1) screening for renal disease and level of renal function, (2) recognizing specific renal and electrolyte disorders, and (3) approaching patients with impaired renal function. The section on handling patients on hemodialysis is most useful.

Drs. Izenstein, Dluhy and Williams in the chapter on endocrinology examine the physiologic and pathophysiologic events associated with disease of the endocrine glands and present guidelines for medically preparing patients with such diseases for operation.

The chapter on hematology covered by Drs. Cooper and Churchill presents many details regarding the evaluation and management of several hematological problems. Topics of special concern to anesthesiologists include thrombocytopenia, qualitative platelet abnormalities, evaluation of the prolonged partial thromboplastin time, use of low doses of heparin and preparation of patients taking anticoagulants for operation.

Dr. Dawson in the chapter on neurologic disease reviews several neurological diseases that may be of concern when evaluating patients preoperatively. These include the myopathies, peripheral neuropathies, Parkinson disease, multiple sclerosis, cerebrovascular disease, convulsive disorders, metabolic encephalopathy and cerebral edema, and alcoholism. He warns, "*Every* alcoholic ought to receive 50 to 100 mg of thiamine HCl intramuscularly as a precautionary measure before glucose is administered."

In the dental and oral surgical chapter Dr. Kaban reviews common dental and oral surgical problems that may present in preoperative patients. Of particular interest are his comments regarding patients with temporomandibular joint dysfunction, chronic hypomobility of the jaw and chronic dislocation of the mandible.

Finally, the psychiatric preparation of surgical patients is reviewed by Drs. Kelly and Reich. They stress careful assessment of commonly seen preoperative psychiatric problems and suggest simple preventive and therapeutic measures available to the medical and surgical team. Their suggestions regarding handling psychiatric drugs are especially appropriate.

This book can be both useful and pleasant if read in its entirety, or it can be used as a quick reference when problems arise. Brief marginal summaries of each page stress salient points. The index is ample—simplifying looking up special problems in a hurry. Each chapter contains many gems of information which will help the anesthesiologist to carry out better his mission of acting as the "internist in the operating room."

All chapters appear up-to-date, crisp and apparently specifically written for this book. Because this is not a full textbook of medicine, readers may wish to consult the more detailed reference to the recent literature appended at the end of each chapter, which contain several 1978 and 1979 citations.

Residents confronted with unusual medical problems in their sick surgical patients will find this book useful in preparing for their preoperative evaluations or their preanesthesia conferences. Because board examinations now emphasize the integration of knowledge of diseases and changes produced by anesthesia, residents will profit from reading this text while preparing for boards in anesthesia or surgery.

In summary, this unique erudite textbook well addresses a problem too long ignored—how to make the patient ready for anesthesia.

CARTER M. BALLINGER, MD

Professor of Anesthesiology
University of Colorado Health Sciences Center
Denver

in memoriam

California Medical Association

BYRNE, RALPH V., Los Angeles. Died January 19, 1981, aged 76. Graduate of St. Louis University School of Medicine, 1930. Licensed in California in 1938. Dr. Byrne was a member of the Los Angeles County Medical Association.

DUNKLEE, GEORGE KINNEY, San Luis Obispo. Died February 5, 1981 in San Luis Obispo, aged 87. Graduate of the University of Colorado Medical School, Denver, 1917. Licensed in California in 1930. Dr. Dunklee was a retired member of the San Luis Obispo County Medical Society.

FROST, ARTHUR J., Long Beach. Died December 6, 1980, aged 70. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1938. Licensed in California in 1938 MD degree from California College of Medicine, 1962. Dr. Frost was a member of the Los Angeles County Medical Association.

GLASSMAN, SAMUEL C., Los Angeles. Died October 7, 1980, aged 80. Graduate of the University of California Medical School, Berkeley-San Francisco, 1926. Licensed in California in 1926. Dr. Glassman was a member of the Los Angeles County Medical Association.

GRANT, REUBEN S., Sherman Oaks. Died November 21, 1980, aged 73. Graduate of the Marquette University School of Medicine, Milwaukee, 1933. Licensed in California in 1940. Dr. Grant was a member of the Los Angeles County Medical Association.

JONES, GLEN E., Los Angeles. Died January 25, 1981, aged 70. Graduate of the University of Arkansas School of Medicine, Little Rock, 1938. Licensed in California in 1939. Dr. Jones was a retired member of the Los Angeles County Medical Association.

KROGER, WILLIAM P., Los Angeles. Died January 31, 1981, aged 88. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1918. Licensed in California in 1921. Dr. Kroger was a retired member of the Los Angeles County Medical Association.

LANDIS, RAYMOND A., Los Angeles. Died in September 1980, aged 76. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1929. Licensed in California in 1929. MD degree from California College of Medicine, 1962. Dr. Landis was a retired member of the Los Angeles County Medical Association.

NERAD, ANTON H., San Luis Obispo. Died December 19, 1980, aged 90. Graduate of the University of Minnesota Medical School, Minneapolis, 1920. Licensed in California in 1920. Dr. Nerad was a retired member of the Los Angeles County Medical Association.

SCHLUETER, FRANCIS EDWARD, Pasadena. Died January 5, 1981, aged 64. Graduate of Northwestern University Medical School, Chicago, 1940. Licensed in California in 1945. Dr. Schlueter was a member of the Los Angeles County Medical Association.

STRAHAN, LOLIN ROBERT, Paso Robles. Died February 6, 1981 in Templeton, aged 77. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1928. Licensed in California in 1928. MD degree from California College of Medicine, 1962. Dr. Strahan was a retired member of the San Luis Obispo County Medical Society.

VINNECOUR, MAX I., Los Angeles. Died in January 1981, aged 75. Graduate of Tufts College Medical School, Boston, 1928. Licensed in California in 1945. Dr. Vinnecour was a member of the Los Angeles County Medical Association.

WOODHULL, CLAYTON G., Palmdale. Died December 16, 1980, aged 86. Graduate of Detroit College of Medicine and Surgery, 1917. Licensed in California in 1924. Dr. Woodhull was a member of the Los Angeles County Medical Association.

New Mexico Medical Society

HOLLE, LARRY A., Chama. Was killed March 3, 1981 in Colorado in a skiing accident, aged 39. Graduate of the Washington University School of Medicine, St. Louis, 1967. Licensed in New Mexico in 1971. Dr. Holle was a member of the New Mexico Medical Society.

SEIBERT, VIRGIL EVERET, Albuquerque. Died January 29, 1981, aged 60. Graduate of Loyola University School of Medicine, Chicago, 1944. Licensed in New Mexico in 1951. Dr. Seibert was a member of the Albuquerque & Bernalillo Medical Society.

WELLS, EMERY I., Albuquerque. Died March 19, 1981 in Albuquerque, aged 76. Graduate of the University of Modena School of Medicine, Italy, 1932. Licensed in New Mexico in 1971. Dr. Wells was a member of the Albuquerque & Bernalillo Medical Society.

Utah State Medical Association

HORTON, WALTER HAROLD, Salt Lake City. Died February 6, 1981 in Salt Lake City, aged 78. Graduate of Louisiana State University School of Medicine, New Orleans, 1937. Licensed in Utah in 1937. Dr. Horton was a member of the Salt Lake County Medical Society.

LIPPINCOTT, STUART W., Layton. Died January 19, 1981 in Sun City, Arizona, aged 73. Graduate of the McGill University Faculty of Medicine, Montreal, 1935. Licensed in Utah in 1974. Dr. Lippincott was a member of the Davis County Medical Society.

works well in your office...

NEOSPORIN® Ointment

(polymyxin B-bacitracin-neomycin)

Each gram contains: Aerosporin® (Polymyxin B Sulfate) 5,000 units, bacitracin zinc 400 units, neomycin sulfate 5 mg (equivalent to 3.5 mg neomycin base); special white petrolatum qs; in tubes of 1 oz and 1/2 oz and 1/32 oz (approx.) foil packets.

works just as well in their homes.

- It's effective therapy for abrasions, lacerations, open wounds, primary pyodermas, secondarily infected dermatoses.
- It provides broad-spectrum overlapping antibacterial effectiveness against common susceptible pathogens, including staph and strep.

- It helps prevent topical infections, and treats those that have already started.
- It contains three antibiotics that are rarely used systemically.
- It is convenient to recommend without a prescription.

NEOSPORIN® Ointment—for the office, for the home.

(polymyxin B-bacitracin-neomycin)

Effective • Economical • Convenient • Recommendable

Each gram contains: Aerosporin® (Polymyxin B Sulfate) 5,000 units, bacitracin zinc 400 units, neomycin sulfate 5 mg (equivalent to 3.5 mg neomycin base); special white petrolatum qs; in tubes of 1 oz and 1/2 oz and 1/32 oz (approx.) foil packets.

WARNING: Because of the potential hazard of nephrotoxicity and ototoxicity due to neomycin, care should be exercised when using this product in treating extensive burns, trophic ulceration and other extensive conditions where absorption of neomycin is possible. In burns where more than 20 percent of the body surface is affected, especially if the patient has impaired renal function or is receiving other aminoglycoside antibiotics concurrently, not more than one application a day is recommended.

When using neomycin-containing products to control secondary infection in the chronic dermatoses, it should be borne in mind that the skin is more liable to become sensitized to many substances, including neomycin. The manifestation of sensitization to neomycin is usually a low grade reddening with swelling, dry scaling and itching; it may be manifest simply as a failure to heal. During long-term use of neomycin-containing products, periodic examination for such signs is advisable and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for that patient thereafter.

PRECAUTIONS: As with other antibacterial preparations, prolonged use may result in overgrowth of non-susceptible organisms, including fungi. Appropriate measures should be taken if this occurs.

ADVERSE REACTIONS: Neomycin is a not uncommon cutaneous sensitizer. Articles in the current literature indicate an increase in the prevalence of persons allergic to neomycin. Ototoxicity and nephrotoxicity have been reported (see Warning section).

Complete literature available on request from Professional Services Dept. PML.

Wellcome

Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

(Continued from Page 24)

PHYSICIANS WANTED

FAMILY PRACTICE PHYSICIAN needed to work with a young Board Certified Family Practitioner in the beautiful Panhandle of North Idaho. Excellent specialty backup is available. Corporate benefits include a generous pension plan, excellent vacation and CME opportunities and a competitive salary. Applicant must like hard work and be willing to do obstetrics. Write Box 6188 Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

WANTED: Holistic physician nutritionally oriented to share office on part-time basis. Virginia Flanagan, MD, 13320 Riverside Dr., #112, Sherman Oaks, CA 91423. Phone (213) 995-4233.

SAN FRANCISCO BAY AREA: Three-man Family Practice group seek recent board-certified Family Practitioner for busy office. Attractive salary plus incentive, full fringes, 6 weeks vacation, and C.M.E. Send résumé to Philip R. Hines, MD, Inc., 220 Hospital Dr., Vallejo, CA 94590.

SOUTHERN CALIFORNIA REGIONAL DIRECTOR—Would prefer physician with background in either preventive or internal medicine. Expected to assume both clinical and administrative duties within corporate medical department and Southern California area. Salary commensurate with qualifications and experience. Send résumé to Reynold T. Schmidt, MD, Box 7600, Los Angeles, CA 90051.

EMERGENCY MEDICINE OPPORTUNITIES, full and part-time, in the Rocky Mountain states for career oriented emergency physicians. Excellent compensation and paid professional liability insurance. Send credentials to Mr. William Salmo, Chase Stone Center, Holly Sugar Building, Suite 440, Colorado Springs, CO 80903. Or call toll-free 1 (800) 525-3681 (in Colorado call collect (303) 471-4981).

SAN FRANCISCO KAISER-PERMANENTE MEDICAL CENTER. Full-Time Temporary Internist needed immediately for General Medical duties. Call collect—Dr. Fessell, (415) 929-4740.

INTERNAL MEDICINE—OREGON. Fastest growing community on Oregon Coast looking for 1-2 internists to join existing medical staff of 7 FP's and 1 surgeon. Excellent recreation opportunities—hunting, fishing, boating, etc. 47-bed hospital is 1¼ hours away from 400-bed medical center. Beautiful location. 12,000 population service area. Contact Doug Kunsman, Administrator, Western Lane Hospital, P.O. Box 580, Florence, OR 97439. (503) 997-3468.

ORTHOPEDIC SURGEON to join multispecialty group in Mt. Vernon, Washington. The Medical Center has outstanding x-ray facilities and is located across the street from a 126-bed hospital. Stockholder status available after one year. Guaranteed first year salary and liberal fringe benefits. On call coverage available. Position currently availabe. Contact Shane Spray, Administrator, Skagit Valley Medical Center, 1400 E. Kincaid, Mt. Vernon, WA 98273. Telephone (206) 428-2524.

WANTED: PEDIATRICIAN/OB/GYN/GENERAL INTERNIST—Board certified or eligible—To associate with expanding 8-man group of Multispeciality Physicians in Tacoma, Washington—Salary $40,000 per annum with partnership after first year. Send curriculum vitae or inquiries to: Clinton F. Merrill, MD, Puget Sound Clinic, 3611 South "D" Street, Tacoma, WA 98408. Or phone collect: (206) 756-8591 or (206) 589-9499 (after hours).

INTERNIST: Board Certied or eligible internist, to join well-established 3-man group of internists in San Jose, California. Office near excellent general hospital. Guaranteed salary first year. Incremental partnership thereafter. Send CV to Box 6196, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PHYSICIANS WANTED

ANESTHESIA—FRESNO, CALIFORNIA. The Valley Medical Center of Fresno, in affiliation with the UCSF School of Medicine, seeks two anesthesiologists for its Department of Anesthesia. The Valley Medical Center, a 400-bed county facility, is the principal teaching hospital of the Medical School's new clinical branch in Fresno. The positions offer excellent opportunities in clinical anesthesia, teaching and research; competitive salary. Board Certification or eligibility and California license required. Please send inquiries to: Frank L. Davidson, MD, Chief of Anesthesiology, Valley Medical Center, 445 S. Cedar Avenue, Fresno, CA 93702, (209) 453-4496.

KING CITY, MONTEREY COUNTY, CALIFORNIA: "STEINBECK COUNTRY"—8-man multispecialty group is looking for 2 Family Practitioners-FP's must be willing to take OB's. Ability to speak Spanish helpful but not mandatory. King City is located 1 hr. from Monterey Peninsula and 3 hrs. from San Francisco. Excellent fringe benefits, 1st year guaranteed minimum salary, opportunity to join corporation after 6-12 months. Send CV or contact: Allan L. Fisher, MD, or Lee S. Roberts, Admin. SoMoCo Medical Group, 210 Canal St., King City, CA 93930, or telephone (408) 385-5471.

FAMILY PRACTITIONER—Position available in a growing and dynamic pre-paid health care plan in Spokane, Washington. This is an unusual opportunity to practice comprehensive family medicine with other well trained family practitioners without many of the distractions of office management. Continuity of care, patient education/preventative medicine, and high quality personal-style care are emphasized. Excellent salary and benefits. Ample cultural, educational, and recreational resources in our city and the surrounding countryside. Address inquiry and/or CV to James Shaw, MD, INA Healthplan of Washington, North 3919 Maple Street, Spokane, WA 99205.

IDAHO—FAMILY PRACTICE. Three Physician Clinic, Opening 6/1/81, University Community, Salary Negotiable, Contact D. E. Adams, MD, Moscow Clinic, P.A., Moscow, ID 83843. Tel. (208) 882-7565.

GENERAL SURGEON: Bd elg./cert. needed by 8-man multispecialty Group in King City, Monterey County, California, "Steinbeck Country." King City is 1 hr. from Monterey Peninsula and 3 hrs. from San Francisco. Excellent fringe benefits, opportunity to join Corp. after 6-12 months. Send CV or contact: Allan L. Fisher, MD, or Lee S. Roberts, Administrator, at Southern Monterey County Medical Group (A professional Corporation), 210 Canal St., King City, CA 93930, (408) 385-5471.

GROW WITH US IN SUNNY ARIZONA—The INA Healthplan needs physicians in family practice and most specialties in Tucson and Phoenix. Attractive salaries and comprehensive benefits including a professional development program, retirement plan, and group incentive bonus are provided. If team interaction and casual living appeal to you, send your CV to: Professional Relations, INA Healthplan, Inc., 6115 North 7th Street, Phoenix, AZ 85014.

ORTHOPEDIC SURGEON—Board Certified, Orthopedic Surgeon needed at VA Medical Center, Livermore, CA. Ideal living, good climate and clean air. Malpractice insurance not needed. Position available at present. Salary dependent upon experience and qualifications. Contact: John F. Kane, MD, Chief of Staff, VA Medical Center, Livermore, CA 94550. Tel: (415) 447-2560, ext. 204.

LARGE CONSULTING GROUP in pulmonary medicine seeking physicians trained in pulmonary and infectious diseases or allergy to practice in Northern California in June 1981 or 1982. Applicants please send CV to Box 6195, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

(Continued on Page 36)

FAMILY PRACTICE

Family practitioner (preferably with obstetrics) to join a family practice in a small rural community in the Sierra Foothills. Applicant should be willing to work with family nurse practitioners and/or physician assistants. Guaranteed salary, excellent fringes and profit sharing. Excellent recreation and vacation facilities, liberal time off.

Contact:

Mr. W. E. ROSE, Jr., Administrator

Phone (209) 781-4100 EXT 510

FLAGSTAFF MEDICAL BUILDING LEASE AND OWN

Located next to the Flagstaff Hospital and Medical Center on the corner of Forest and Beaver Streets. A Pharmacy, laboratory and radiology in the complex plus parking easily accessible to either your office or the hospital makes the Flagstaff Medical Building the desired choice for the largest number of practicing physicians in any medical building located in Northern Arizona. Your customized medical office suite (ranging from 800 to 2,000 sq. ft.) is now available at a most reasonable cost plus the existing partnership is now offering those tenants signing leases before May 15, 1981 the opportunity to purchase an ownership interest in the building. Please contact:

BRUCE O. UTTERBACH, CPM, FLAGSTAFF MEDICAL BUILDING, 1355 N. BEAVER, FLAGSTAFF, ARIZONA 86001. (602) 774-4416.

FAMILY PRACTICE PHYSICIANS

Unique opportunity for you to associate with our medical group which currently operates many FPs throughout Southern California. Independent practice setting with no investment/cost concerns. Substantial guarantee, profit sharing program, malpractice provided.

For further information, contact

PACIFIC PHYSICIAN SERVICES
P.O. Box 1346
Loma Linda, CA 92354
(714) 825-4401

DEVELOPMENTAL DISABILITIES PROGRAMS

Opportunities are available for internists, family practitioners and psychiatrists to work with developmentally disabled people in State residential communities. Locations from Los Angeles to northern California. Challenging and varied cases, congenial professional environment, excellent civil service benefits.

Hospital Recruitment Program
Dept. of Developmental Services
714 P Street
Sacramento, CA 95814
(916) 322-1221 collect

Read across specialty lines.

Each month the WESTERN JOURNAL provides an excellent, quick way for busy physicians to keep abreast of what is happening in other fields of medicine. It seeks also to offer a balanced fare of scientific and social progress, with something in every issue for students, scholars, practitioners, academicians, researchers and Medicine's political leaders.

The WESTERN JOURNAL lets you read across specialty lines.

THE WESTERN
Journal of Medicine

Please mail this coupon with enclosed payment to:
THE WESTERN JOURNAL OF MEDICINE—Circulation Department
731 Market Street, San Francisco, California 94103

WJ5/81

Subscriptions, U.S. and Canada $10 All other countries $18

Enclosed is $_____ to cover _____ subscriptions. Subscription renewal ☐

Send subscription

TO: _____

_____
Street

_____
City State Zip

_____
Specialty

Gift Card to read "From _____"

Regular subscription ☐ Foreign subscription ☐

TO: _____

_____
Street

_____
City State Zip

_____
Specialty

Gift Card to read "From _____"

Regular subscription ☐ Foreign subscription ☐

(Continued from Page 34)

PHYSICIANS WANTED

PULMONARY PHYSICIAN: Needed immediately to join a group of active internists in suburb of Los Angeles. Attractive salary and fringe benefits. Send CV to Box 6197, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

CARDIOLOGIST WANTED: A full time position is now available as assistant director of a comprehensive cardiac unit located in a hospital in the suburbs of Los Angeles. Duties will include performance of all invasive and non-invasive cardiac procedures including two dimensional echocardiography, pacemakers and cardiac catheterization. Some clinical work will be involved in assisting the director in his day to day practice and providing some night time and weekend coverage. Excellent salary and fringe benefits including retirement plan, paid vacation and educational leave. Please send CV to Box 6198, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PEDIATRICIAN. A progressive 75-bed non-profit acute hospital, 35 miles north of San Francisco, has the need for a pediatrician with neonatal experience, to develop and head up an inpatient and outpatient pediatrics service. Physician community and hospital are prepared to assist in practice development. Box 6199, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

CARDIOLOGIST: Invasive and Non-Invasive needed for busy cardiology practice in the beautiful Pacific Northwest. Includes active open heart surgery program, requires catheterization, pacemakers and all non-invasive modalities. Please reply with CV to Box 6200, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

ORTHOPEDIC SURGEON—to join 45 person multi-specialty group with four locations in San Diego. Board certified or eligible. Full clinical services available. CME approved group. Partnership possible in (2) years. Guaranteed salary first (2) years with excellent future opportunity. Start immediately. Rees-Stealy Medical Group, 2001 4th Ave., San Diego, CA 92101. (714) 234-6261, H. D. Peabody, MD.

OBSTETRICAL ANESTHESIOLOGIST NEEDED. Work also available in GYN surgery and pain clinic. Board eligible or certified. Fee for service. Join three obstetrical anesthesiologists in new 370 bed hospital. Excellent recreational area. Contact Turhan S. Dogu, MD, McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden, Utah 84409. Telephone (801) 627-2800.

FINANCIAL REWARDS
and
PROFESSIONAL SATISFACTION . . .
. . . plus a whole lot more, Doctor!

We offer physician salaries in all specialties including General Practitioner and Family Practitioner that are among the highest paid in the nation and our benefit package (including malpractice insurance) is unexcelled.

Our quality of care is excellent; our medical facilities are attractive and efficient; and our climate for both living and working is outstanding.

We are one of the largest Federally-approved HMO's in the U.S., and we currently have a few very desirable positions available in the Los Angeles area. If you are interested, please call or write:

INA HEALTH PLAN OF CALIFORNIA
1880 Century Park East
Los Angeles, CA 90067

Phone (213) 553-6677, Extension 364

Attn.: Mr. Yoakam
Director of Physician Services

PHYSICIANS WANTED

GENERAL INTERNIST. Excellent opportunity with well established 2-man private practice association in sophisticated medical community. Contact David L. Davis, MD, 1400 Florida Ave., Modesto, CA 95350. (209) 527-5063.

SPOKANE, WASHINGTON: Position available in very busy emergency department—25,000 visits per annum—teaching opportunities. Looking for career oriented Emergency Physician who is board certified in either general surgery, external medicine, family practice or emergency medicine. Individual contract, excellent income and benefits. Contact: K. Murphy, Emergency Department, Sacred Heart Medical Center, West 101-8th Ave., TAF-C9, Spokane, WA 99220. (509) 455-3344.

CALIFORNIA—FAMILY PRACTITIONERS/INTERNISTS needed for primary care group practices in fast-growing areas. Excellent professional support staff, modern facilities, percentage of gross income with guaranteed minimum income. Benefits include: Paid malpractice, health and life insurance, CME leave, etc. Send CV to S. Lee, Medicenters, P.O. Box 8013, Fresno, CA 93747. (209) 252-1618.

POSITION IN ONCOLOGY: The Department of Medicine, University of California, San Francisco, is seeking a medical oncologist certified in Internal Medicine and qualified for Oncology boards for an Assistant Professor position effective July 1, 1981. Responsibilities include organization and implementation of a strong clinical service in oncology and the development of teaching and consultation conferences at San Francisco General Hospital. The University of California is an Equal Opportunity/Affirmative Action Employer. Please contact Merle A. Sande, MD, San Francisco General Hospital, Room 5H22, San Francisco, CA 94110.

UNIQUE FAMILY PRACTICE FACULTY POSITION. UCSF affiliate family practice residency, Fresno, California. Offers teaching/clinical responsibilities at model rural practice site. Send CV and request to John Blossom, MD, Valley Medical Center, 445 So. Cedar Ave., Fresno, CA 93702. (209) 453-5705.

CHEST PHYSICIAN—Position available for full-time chest physician in Pulmonary Disease Service. Requiring qualifications in clinical management, laboratory supervision, consultation, fiberoptic bronchoscopy, and teaching involvement with medical students, interns, and residents. American Board of Internal Medicine certification or eligibility, and California State license necessary. Completion of pulmonary Fellowship desirable. Salary and university faculty appointment negotiable according to credentials. Equal opportunity employer—Women and minority groups invited to apply. If interested, please submit curriculum vitae to: D. Armin Fischer, MD, Rancho Los Amigos Hospital, 7601 E. Imperial Hwy., Room 16, Bldg. 500, Downey, CA 90242.

CARDIOLOGIST, Board certified or eligible trained in heart catheterization for four-man cardiology group, affiliated with large Cardiovascular Center. Referral practice located near Los Angeles. University affiliation available. Immediate partnership, nothing to buy. Equal work, pay and time off. Must speak fluent American. Call (213) 866-3716.

CALIFORNIA: The State Department of Social Services' Disability Evaluation Division is currently accepting applications for Medical Consultant I positions in Los Angeles, San Diego, Fresno, Oakland and Sacramento. These positions offer a competitive salary, generous fringe benefits and an excellent retirement program. A California license is required. For further details, please contact: Mr. Anthony Roullier, 1414 "K" St., Rm 204, Sacramento, CA 95814. Tel (916) 323-8667.

ORTHOPEDIC SURGERY
OB/GYN
OTOLARYNGOLOGY
GENERAL SURGERY

We have immediate need of physicians in these and other disciplines to join us at INA/Ross-Loos Healthplan, now marking a half-century of service to Southern California members.

INA/Ross-Loos health centers are located throughout the region providing comprehensive care through utilization of community hospitals.

We offer the board eligible/certified physician an opportunity to grow with us in an environment of challenge, freedom from malpractice premiums, minimized paperwork and excellent fringe benefits.

Our compensation is highly competitive. Request details by phone or letter to:

ROSS LOOS MEDICAL GROUP, INC

ALLAN S. MIRKEN, MD
Director of Medical Personnel
INA/Ross-Loos Medical Center
1711 West Temple Street
Los Angeles, CA 90026
(213) 413-1313

PHYSICIANS WANTED

PEDIATRIC-INTENSIVIST: Strong intensive care experience. Send CV to Chairman, Department of Pediatrics, Santa Ana-Tustin Community Hospital, 1001 No. Tustin Ave., Santa Ana, CA 92705. (714) 835-3555, ext. 3703.

CALIFORNIA, SAN JOSE: Experienced Emergency Physician with Spanish-speaking ability preferable, wanted to join our group practicing in San Jose at a University-affiliated medical center and two community hospitals. Total patient volume of 90,000; fee-for-service compensation. If interested, send CV or contact: James B. Lane, MD, 1541 The Alameda, 2nd floor, San Jose, CA 95126. Phone (408) 293-8881.

CALIFORNIA, SAN JOSE: Primary Care Physician with experience in minor trauma and Peds. wanted to staff ambulatory care clinic at large teaching hospital in San Francisco Bay Area. Flexible hours, independent contractor status with hourly compensation. For further details, please call or write: Eve Campbell, 1541 The Alameda, 2nd floor, San Jose, CA 95126. Tel: (408) 293-8881.

PHYSICIANS NEEDED in rapidly growing Tri-Cities area, especially internists, family practitioners, and pediatricians. Solo and group situations available. Call collect—Raymond Kerr, MD, (509) 582-5137, Kennewick, WA.

NEW MEXICO—NORTHWESTERN: Opportunity available for a physician interested in providing primary care in this modern clinic open 8 a.m.-5 p.m., Monday-Friday. Guaranteed income, liability insurance provided. For details, send credentials to William Salmo, Chase Stone Center, Holly Sugar Building, Suite 1070, Colorado Springs, CO 80903; or call toll-free 1 (800) 525-3681 (in Colorado call collect (303) 471-4981).

NEBRASKA EMERGENCY MEDICINE: Directorships and clinical positions available in several moderate volume emergency departments located in the western and central portions of the state. Excellent guaranteed income, plus additional stipend for directors' duties. Professional liability insurance provided; flexible scheduling without on-call involvement. For details, forward credentials in confidence to William Salmo, Chase Stone Center, Holly Sugar Building, Suite 1070, Colorado Springs, CO 80903; or call toll-free 1 (800) 525-3681 (within Colorado call collect (303) 471-4981).

PHYSICIANS WANTED

DIRECTOR OF CLINICAL SERVICES for Santa Barbara County Health Care Services, a progressive health care delivery organization. A full-time position. Board certification in Internal Medicine or Family Practice. Duties include supervision and staffing of county clinics throughout Santa Barbara County. Physician will also be responsible for Quality Care Assurance and on-going CME Programs. Competitive salary. Send CV and 3 letters of reference to Robert D. Marvan, MD, Director of Clinical Services, Santa Barbara County Health Care Services, 300 San Antonio Road, Santa Barbara, CA 93110. Phone (805) 967-2311, ext. 240.

STUDENT HEALTH PHYSICIAN. Beginning September 1, 1981, an opening at Humboldt State University for a physician experienced in primary care. Must be licensed to practice medicine and surgery in California. 6,500 students; 10 month (academic year) position, 40 hour week, out-patient clinic, no nights. Excellent benefits. Salary $36,430-43,880. Submit letter of application, vitae, three letters of reference and a statement of philosophy of student health care to: J. A. Corbett, MD, Director Student Health, Humboldt State University, Arcata, CA 95521, or for more information call (707) 826-3146. Application deadline July 1, 1981.

ASSOCIATES WANTED

FAMILY PHYSICIAN or other primary care: To associate with long-established board certified FP. Recent ultra-modern medical office in high income area of Orange County. Major hospital close by. Community college and Calif. State Univ. In area, teaching—UCI. Write Box 6155, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

SITUATIONS WANTED

WOMAN PHYSICIAN in early sixties, in good health, seeks part-time position, 1-2 days/week, in psychiatry and/or general medicine in Catholic hospital, institution or office within 50 mi. radius of San Francisco or Truckee in California. Practice must be under physician willing to supervise, as probationary requirement of BMQA. Write to: Physician, Box 6165, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

ORTHOPEDIC SURGEON. 52 years old. Board certified. Interested in office orthopedics and/or evaluations of disabilities. Part or full time. Write Box 6191, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

INTERNIST, board-eligible, 30, family practice experience, seeks associateship or small group practice in Northern California or Southern Oregon. Available Mid-July, 1981. Ted W. Grace, MD, 2700 S. Holly St. Unit 205, Denver, CO 80222.

OPTICIAN: California Registered Optical Dispenser desires to relocate dispensary and finishing lab near 2 or more non-dispensing Ophthalmologists. Southern Calif. area preferred but not a necessity. Box 6190, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

LEGAL COUNSEL

SAMUEL SPITAL, ESQ.
1200 Third Avenue, Suite 1200
San Diego, CA 92101, (714) 231-4848

Former DEPUTY ATTORNEY GENERAL representing the Board of Medical Quality Assurance and Dept. of Health. Now specializing in B.M.Q.A. and defense malpractice matters throughout California.

SITUATIONS WANTED

FAMILY PRACTITIONER board qualified. Licensed California, Oregon, Washington, Minnesota. Age 47. Interested in all opportunities, prefer group practice, ER work, Industrial medicine, metropolitan or rural practice. Full or part time. Contact Robert L. Stein, MD, 1215 First Ave., No. Sauk Rapids, MI 56379. Tel (612) 255-0467.

INFECTIOUS DISEASE-INTERNIST. University trained, 30, ABIM certified. ID Board eligible. Desires opportunity in Infectious Disease/Internal Medicine in or near San Diego. Available July 1981. N. Kollisch, MD, 33 Pond Ave., Brookline, MA 02146. Tel (617) 566-0875.

INTERNIST/ENDOCRINOLOGIST—35, board certified in both. Excellent background. Looking for practice opening in Northern California. Box 6201, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

DIAGNOSTIC RADIOLOGIST—Experienced in ultrasound, CT, nuclear medicine, angio, seeking full time position. Strong preference for central valley. ABR certified. Reply Box 6202, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PEDIATRIC CARDIOLOGIST—Board certified or eligible; private practice—California. Reply with curriculum vitae to Box 6203, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PHYSICIAN'S ASSISTANT, 27, certified nationally in primary care and surgery, ACLS, graduate of postgraduate surgical internship, and fully trained in cardiothoracic surgery at major university hospital, seeks private or institutional affiliation. Geographic preference in sunbelt. Available July 1981. Contact John Lee, 3450-13D Wayne Ave., Bronx, NY 10467.

OPHTHALMOLOGIST, 30, married, completing excellent midwestern residency. Seeking association with group or individual, or beginning solo practice in community with need. Available July 1981 or later. Contact Jay Lavine, MD, 10308 Briar Hollow, No. 11, St. Louis, MO 63141.

SOUTH BAY INTERNIST seeks local part-time (40-70 percent) private practice affiliation. ABIM, board qualified infectious disease, gynecology experience. Age 33, practicing 5 years. Contact Box 6204, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

LOCUM TENENS WANTED

LOCUM TENENS: Prestigious Sports Medicine/Preventive Medicine Center needs a board certified internist experienced in Stress Testing and giving complete physicials for one month, anytime early 1981. Write Box 6182, Western Journal or Medicine, 731 Market St., San Francisco, CA 94103.

LOCUM TENENS SERVICE: Western Physicians Registry offers coverage for vacation or continuing education. To participate as temporary physician or to arrange coverage for your practice, contact: Carol Sweig, Director, 1124 Ballena Bl., Alameda, CA 94501. (415) 521-4110.

LOCUM TENENS WORK WANTED

45-YEAR ABFD available for short term locum (1-3 weeks). No surgery or OB. Strong internal medicine background. Willing to go anywhere in California. Valid Calif. and BDDN Licenses. James F. Donovan, 5055 Marlin Way, Oxnard, CA. (805) 985-4435.

MEDICAL EQUIPMENT FOR SALE

IE INDUSTRIAL doctor's exam table in excellent condition. $500. (415) 897-7121.

PSL

PRACTICE SALES & LOCATIONS

PRACTICES FOR SALE

All specialities available. Request practice list.

NEW OFFICE SET-UPS

Locations for lease, lease w/equity, purchase.

APPRAISALS

Practice appraisal for buyouts, dissolutions, etc. Widely accepted as the most comprehensive and rational.

PRACTICE SALES & LOCATIONS, INC.

17942 Skypark Circle, Suite D
Irvine, CA 92714

(714) 641-9203

PRACTICES AVAILABLE

PRACTICE SALES, PLACEMENT—Orthopedics, OB/GYN, Dermatology, Internal, Family, Pediatrics, Ophthalomology, ENT, etc. Partnerships, Appraisals. Professional Practice Opportunities, 21 Altamount Dr., Orinda, CA. (415) 376-0762.

BUYING or SELLING any type Medical Practice contact California Professional Practices, 2555 Huntington Dr., Suite D, San Marino, CA 91008. (213) 796-9262 or Agent Mr. Reilly (805) 543-4782 or Cliff Rauch (714) 997-0853.

1,000 SQUARE FEET finished to occupy 4 exams, laboratory, reception plus 1,000 available to develop. $7 sq. ft. plus utilities. Dentists other occupant. Five Mile Med Dental Bldg, Spokane, WA; Elaine K. Glover, MD, 1625 W. Francis, Spokane, WA 99208. (509) 327-1503, (509) 466-6428.

PRACTICE FOR SALE

SEATTLE—GERIATRIC PRACTICE for sale. Ideal for part-time or startup practice. Available 8/1/81. $35-45,000 net. Reply with CV to Box 6205, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

MEDICAL SPACE TO SHARE

RENTAL (OFFICE): South Orange County, California. Sub specialized or gen. surgeon or GP to pro rata share 1,520 sq. ft. new modern, fully equipped medical suite, in large hosp. complex. Ideally loc. adj. all maj. hosp., recreation, countryside. Please call and send CV with photo to: Robert L. Epps, MD, 23961 Calle de la Magdalena, #300, Laguna Hills, CA 92653. Telephone (714) 770-6679.

OFFICES FOR RENT OR LEASE

WALNUT PANELLED OFFICE in medical-dental building across from John Muir Hospital. Share remainder of suite and waiting room with psychiatrist. Anteroom available for secretary, storage, etc. if desired. (415) 938-8233.

MEDICAL SPACE FOR LEASE

725, 975, or 1,700 sq. ft.
Blossom Hill area—So. San Jose
MAR-LO Investments • (408) 727-1979

CHECKING INTO MEDICAL MALPRACTICE INSURANCE?

CHECK OUT SOME FACTS	NORCAL MUTUAL Insurance Company	Physicians & Surgeons Insurance Exchange	The Doctor's Company
WHICH COMPANY IS DOCTOR OWNED ?	☑	☑	☑
WHICH DOES NOT REQUIRE SUBORDINATED LOAN/SURPLUS CONTRIBUTIONS ?	☑	☑	☐
WHICH IS RETURNING SUBORDINATED LOAN/SURPLUS CONTRIBUTIONS ?	☑	☐	☐
WHICH IS ENDORSED AND SPONSORED BY 24 LOCAL MEDICAL SOCIETIES ?	☑	☐	☐
WHICH HAS THE HIGHEST TOTAL ASSETS AND RESERVES ?	☑	☐	☐
WHICH HAS A SYSTEM OF PREMIUM CREDITS TOWARD RETIREMENT ? *	☑	☐	☐

NORCAL offers coverage to northern California physicians.

If you want more facts, call us toll-free at (800) 652-1051.

Or, call your Medical Society. They've been checking into medical malpractice insurance for years.

NORCAL MUTUAL INSURANCE COMPANY
333 Market Street, San Francisco, CA 94105
(415) 777-4200 or (800) 652-1051 (toll-free)

*NORCAL MUTUAL is the only company offering run-off premium credits to retiring physicians insured with the Company less than 5 years.

(Continued from Page 23)

July 8—**Current Concepts in Contraception.** LLU. Wednesday. 4 hrs.

August 8-15—**Reproductive Endocrinology, Infertility and Contraception.** See Of Interest To All, August 8-15.

August 29-September 5—**Concepts in Infertility.** See Of Interest To All, August 29-September 5.

October 26-31—**Review Course in Clinical Obstetrics and Gynecology and Gynecological Histopathology.** Memorial Hospital Medical Center-UCI Center for Health Education at Sheraton, Newport Beach. Monday-Saturday. Contact: Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-2311.

PEDIATRICS

May 15-16—**23rd Annual Pediatric Symposium.** So. Calif. Permanente Medical Group at Hyatt Regency, Los Angeles. Friday-Saturday. Contact: Shirley Gach, SCPMG, Education and Research Dept., 4747 Sunset Blvd., 4th Floor, Los Angeles 90027. (213) 667-4241.

May 20-25—**Pediatrics for the Primary Care Physician and All That Jazz.** UCD at Sacramento. Wednesday-Monday.

May 30—**The Child With Facial Deformity: A Progress Report.** See Surgery, May 30.

September 25-29—**Pediatric Urology.** UCD at Silverado Country Club, Napa. Friday-Tuesday.

October 2-3—**Pediatric Gastroenterology and Nutrition.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday. 10 hrs.

October 18—**The Hearing Impaired: Identification, Counseling and Rehabilitation.** Peninsula Hospital and San Mateo Co. Office of Education at Peninsula Hospital, Burlingame. Sunday. Contact: Les Demme, Peninsula Hosp. and Med. Ctr., 1783 El Camino Real, Burlingame 94040. (415) 697-4061.

PSYCHIATRY

June 3-4—**Brief Therapy.** Dept. of Health, Health Training Center/North, at Chico. Wednesday-Thursday. 12 hrs. Contact: Health Training Center, 5850 Shellmound St., Suite 390, Emeryville 94608. (415) 464-0685.

June 3-4—**Communicating With Schizophrenics.** Dept. of Health, Health Training Center/North, Emeryville. Wednesday-Thursday. 12 hrs. Contact: Health Training Ctr., 5850 Shellmound St., Suite 390, Emeryville 94608. (415) 464-0685.

June 22-26—**Comparative Psychotherapies.** USC at Hotel del Coronado, Coronado. Monday-Friday. 21½ hrs. $250.

June 24-25—**Crisis Intervention.** Dept. of Health, Health Training Center/North, Emeryville. Wednesday-Thursday. 12 hrs. Contact: Health Training Ctr., 5850 Shellmound St., Suite 390, Emeryville 94608. (415) 464-0685.

June 28-30—**Family Problems, Aging and Sexuality.** See Of Interest To All, June 28-30.

July 8-10—**Update in Psychiatry: Psychopharmacology.** UCSD at Hanalei Hotel, San Diego. Wednesday-Friday.

July 31-August 1—**Innovations: New Trends in Family Therapy, Brief Therapy and Family Medicine.** Mental Research Institute at Sheraton-Palace, San Francisco. Friday-Saturday. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

August 15-21—**Neuropsychiatric Issues in the Law, Education and Medicine: Hyperactivity and Dyscontrol Syndrome.** So. Calif. Neuropsychiatric Institute and Hawaii Psychiatric Society at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 15 hrs. Contact: Gail Waldron, MD, 6794 La Jolla Blvd., La Jolla 92037. (714) 454-2102.

RADIOLOGY AND PATHOLOGY

May 24-29—**The Pathologist as a Clinical Consultant.** UCD at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

June 1-4—**Diagnostic Cytology of the Female Genital Tract.** American Society of Clinical Pathologists at San Francisco. Monday-Thursday. 22½ hrs. $450, members; $550, nonmembers. Contact: Marian Macdonald, Admin. Asst., ASCP, 2100 W. Harrison St., Chicago 60612. (312) 738-1336.

June 3-5—**Radiology in the Emergency Room.** UCSF at Golden Gateway Holiday Inn, San Francisco. Wednesday-Friday.

June 5-7—**6th Annual Spring Diagnostic Ultrasound Conference.** L.A. Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. 17 hrs. $290. Contact: John Kassabian, MD, 100 Congress St., Pasadena 91105.

June 16-19—**Society of Nuclear Medicine.** Hilton, Las Vegas. Tuesday-Friday. 28 hrs. $60, members; $120, nonmembers. Contact: Registrar, SNM, 475 Park Ave. S., New York 10016. (212) 889-0717.

July 18-25—**Laboratory Medicine.** USC at Kauai Surf Hotel, Kauai, Hawaii. One week. 29½ hrs. $350.

August 8-15—**Radiology.** USC at Maui Surf Hotel, Maui, Hawaii. One week. 28 hrs. $395.

August 12—**Chest Films—An Indispensable Diagnostic Tool.** LLU. Wednesday. 4 hrs.

August 16-21—**23rd Annual Postgraduate Course in Dermal Pathology.** Memorial Hospital Medical Center-UCI Center for Health Education at Newporter Inn, Newport Beach. Sunday-Friday. Contact: Program Coordinator, Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

August 29-September 5—**Diagnostic Radiology: An In-Depth Seminar Approach to Diagnostic Imaging.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 24 hrs. $345.

September 5-9—**Dermatopathology.** See Medicine, September 5-9.

September 13-17—**Digital Radiology: Clinical Applications and Technical Advances.** STAN. Sunday-Thursday.

September 19—**8th Annual Radiology Symposium.** So. Calif. Permanente Medical Group at Hilton Hotel, Los Angeles. Saturday. Contact: Felecia Madison, SCPMG, Education and Research Dept., 4747 Sunset Blvd., 4th Floor, Los Angeles 90027. (213) 667-4516.

October 8-9—**Fine Needle Aspiration of Breast and Thyroid.** UCSF at Sir Francis Drake Hotel, San Francisco. Thursday-Friday. 13 hrs.

October 8-10—**International Symposium on Medical Virology.** UCI at Disneyland Hotel, Anaheim. Thursday-Saturday. 23 hrs. $100, before Sept. 15; $125, thereafter. Contact: Dr. Luis M. de la Maza, Dept. of Pathology, UCI Med. Ctr., Orange 92668. (714) 634-6868.

Postgraduate Videotape Programs in Diagnostic Radiology. Developed by Dept. of Radiology, UCSF. 27 programs in all aspects of diagnostic radiology. Outstanding national and international guest lecturers in addition to UC staff present basic approaches to radiographic interpretation and technique as well as new research and clinical advances. Contact: Radiology Postgraduate Ed. Section, UCSF, Dept. of Rad., Rm. M396, San Francisco 94143. (415) 666-5731, between 7:00 a.m. and 4:00 p.m.

SURGERY

May 21-23—**Neurosurgery—11th Annual Postgraduate Course.** UCSF. Thursday-Saturday.

May 21-23—**Retina Workshop.** St. Mary's Hospital and Medical Center at Quail Lodge, Carmel Valley. Thursday-Saturday. 12 hrs. Contact: Retina Research Fund, St. Mary's Hosp. and Med. Ctr., 450 Stanyan St., San Francisco 94117.

May 22-23—**Vitrectomy-Ocutome Workshop.** PMC. Friday-Saturday. 12 hrs. $450.

May 30—**The Child With Facial Deformity: A Progress Report.** Plastic Surgery Research Foundation and Children's Hospital and Health Center of San Diego at Vacation Village, San Diego. Saturday. 8 hrs. $75. Contact: Karen Delaney, Plastic Surgery Research Fndn., P.O. Box 33387, San Diego 92103. (714) 272-3126.

June 1-5—**Intensive Course in Refractive Keratoplasty: Barraquer Technique.** Jules Stein Eye Institute, Los Angeles. Monday-Friday. $1,500. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024.

June 5-6—**Ophthalmology Update.** UCD, PMC, UCSF, STAN at Sheraton-Palace, San Francisco. Friday-Saturday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062. (415) 563-4321, ext. 2761.

June 6—**Management of Trauma and Its Complications.** UCD at Sacramento Inn, Sacramento. Saturday. 7 hrs. $65.

June 6-12—**Orthopaedic Review Course.** UCSF at Golden Gateway Holiday Inn, San Francisco. One week.

June 11-12—**Clinical Management of the Infectious Diseases of the Eye: New Developments.** UCSF. Thursday-Friday.

June 12-13—**E.N.T. Workshop.** PMC. Friday-Saturday. 9 hrs.

June 20-27—**Ophthalmology.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. $350.

June 26-27—**Surgery Trauma.** UCLA. Friday-Saturday.

September 9—**New Concepts in the Diagnosis and Management of Peripheral Vascular Disease.** LLU. Wednesday. 4 hrs.

September 18-19—**Ophthalmology Update.** UCD, PMC, UCSF, STAN at Sheraton-Palace, San Francisco. Friday-Saturday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062. (415) 563-4321, ext. 2761.

September 19—**Oxygen Transmission and Extended Wear Contact Lenses.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024.

September 25-29—**Pediatric Urology.** See Pediatrics, September 25-29.

October 11-16—**American College of Surgeons—67th Annual Clinical Congress.** Fairmont and Hilton Hotels, San Francisco. Sunday-Friday. Contact: Fred C. Spillman, Convention Mgr., ACS, 55 E. Erie St., Chicago 60611. (312) 664-4050.

OF INTEREST TO ALL PHYSICIANS

May 16—**Otolaryngology for the Primary Care Physician.** Institute for Medical Education and Research and UCSD at Cafe del rey Moro, San Diego. Saturday. 8 hrs. $70. Contact: Karen Delaney, Inst. for Medical Education and Research, 135 Dickinson St., San Diego 92103. (714) 272-3126.

May 17-22—**Fingers-to-the-Toes: An Orthopedic Approach for the Family Physician.** UCD at Stanford Sierra Lodge, Fallen Leaf Lake. Sunday-Thursday.

May 20—**Asbestos-Related Disease: An Occupational Health Forum for Health Professionals.** Western Institute for Occupational/Environmental Sciences and Herrick Hospital at Veterans Building, San Francisco. Wednesday. Contact: Jane Riggan, Western Inst. for Occupational/Environmental Sciences, 2520 Milvia, Berkeley 94704. (415) 845-6476.

May 30—**Alternative Treatments for Chronic Disease: Integration With Traditional Medical Practice.** PMC. Saturday. 6 hrs. $100.

May 30—**Clinical Perspectives on Street Drugs.** UCLA. Saturday. 6 hrs. $95.

May 31-June 6—**Family Practice Refresher Course.** UCLA at Miramar-Sheraton, Santa Monica. One week.

June 1-5—**8th Annual Family Practice Refresher Course.** UCLA and Santa Monica Hospital Medical Center at Miramar-Sheraton, Santa Monica. Monday-Friday. 37 hrs. $350. Contact: UCLA.

June 7-13—**Family Practice Refresher Course.** UCI at Disneyland Hotel, Anaheim. One week. 53 hrs. Contact: Cont. Ed. in Health Sciences, UCI Extension, P.O. Box AZ, Irvine 92716. (714) 833-5414.

June 8-12—**Family Practice Board Review Course.** UCSF. Monday-Friday.

June 10-12—**6th Annual Conference on Hyperbaric Oxygen.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. Contact: Program Coordinator, Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

June 11-13—**Human Sexuality.** CMA at Claremont Resort, Oakland. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

June 12-14—**Clinical Update.** American Medical Association at Hilton, San Francisco. Friday-Sunday. Contact: AMA Dept. of Meeting Services, 535 N. Dearborn St., Chicago 60610. (312) 751-6000.

June 12-14—**Fifth National Institute of Sports Medicine.** Univ. of Nevada-Reno School of Medicine at MGM Grand Hotel, Reno. Friday-Sunday. 17 hrs. Contact: Jan Douglass, Univ. of Nevada-Reno, Cont. Ed., College Inn, Rm. 336, Reno 89557. (702) 784-4998.

June 26—**Occupational Safety and Health for Hospitals: Keeping a Safe and Healthy Workplace.** PMC. Friday. 6 hrs. $50.

June 28-30—**Family Problems, Aging and Sexuality.** USC. Sunday-Tuesday. 17¼ hrs. $136.

August 1—**Herpes.** UCLA at Memorial Hospital, Long Beach. Saturday.

August 8-15—**Reproductive Endocrinology, Infertility and Contraception—3rd Annual Course.** USC at Royal Lahaina Hotel, Maui, Hawaii. One week. 21½ hrs. $325.

August 15-26—**24th Annual Postgraduate Refresher Course.** USC at Honolulu and Maui. 12 days. 37 hrs. $375.

August 16-21—**9th Annual Family Practice Refresher Course.** UCD at Hyatt Del Monte, Monterey. Sunday-Friday. 36 hrs.

August 29—**The Medical Applications of Exercise.** UCD at El Rancho Racquet Club, Sacramento. Saturday.

August 29-30—**Hemodynamic Monitoring—Pulmonary Artery Catheterization.** Calif. Society of Anesthesiologists at Stanford Univ. Medical Center. Saturday-Sunday. 15 hrs. $275, CSA members; $325, nonmembers. Contact: Richard Manley, CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

August 29-September 5—**Concepts in Infertility—1981—Fifth Annual Edward Tyler Symposium.** Tyler Medical Clinic and Univ. of Hawaii School of Medicine at Royal Lahaina Hotel, Maui, Hawaii. One week. Contact: Frank De Llyls, Astra Tours and Travel, 10929 Weyburn Ave., Los Angeles 90024. (213) 479-4444.

August 30-31—**Orthopedics for the Primary Care Physician.** UCLA at Newporter Inn, Newport Beach. Sunday-Monday.

September 7-18—**Intensive Residency in Occupational Medicine, Session III.** UCSF. Two weeks.

September 19-20—**Eating Disorders.** UCLA. Saturday-Sunday.

September 21-24—**American Academy of Family Physicians.** Convention Center, Las Vegas. Monday-Thursday. 30+ hrs. Contact: Edward E. Daleske, Sec., Committee on Scientific Programs, AAFP, 1740 W. 92nd St., Kansas City, MO 64114. (816) 333-9700.

October 12-14—**Interpretative Enzymology.** UCSD at Sheraton Airport Hotel, San Diego. Monday-Wednesday.

October 12-16—**Hawaii Medical Association—Annual Meeting.** Ilikai Hotel, Honolulu. Monday-Friday. Contact: HMA, 320 Ward Ave., Honolulu 96814. (808) 536-7702.

October 14-15—**Alcoholism and the Family.** PMC at Sheraton at Fisherman's Wharf, San Francisco. Wednesday-Thursday. 12 hrs. $85.

October 18-21—**Sports Medicine Today.** UCD at Stanford Sierra Lodge, Fallen Leaf Lake. Sunday-Wednesday.

October 18-23—**Recognition and Management of Diving Casualties.** UCSD at Travelodge, Harbor Island, San Diego. Sunday-Friday.

October 24—**Psychotherapy: Office Approach for the Primary Care Physician.** UCD. Saturday.

October 28-30—**Workshops in Clinical Hypnosis.** USCD at Village Inn, La Jolla. Wednesday-Friday.

Needs Identification and Fulfillment Tailored to the Individual (NIFTI). UCSF. A new contemporary approach to formal continuing medical education. Participating physicians identify their own CME needs which will be met by a program specifically tailored by UCSF faculty for each individual physician. 25 hrs. minimum; 100, maximum. Fee: $350; $200, UCSF alumni. Contact: Extended Programs in Medical Education, 569-U, Univ. of Calif., San Francisco 94143. (415) 666-4251.

Audio-Digest Foundation—A nonprofit subsidiary of CMA. Provides by subscription twice-a-month tape recorded summaries of leading national meetings and authoritative surveys of current literature. A catalog of lectures and panel discussions in all areas of medical practice is also available. Contact: Audio-Digest Foundation, 1577 E. Chevy Chase Dr., Glendale 91206.

Videotape Postgraduate Course for the Primary Care Physician. UCSF, School of Medicine, Div. of Ambulatory and Community Medicine. 24 Category I hrs. upon completion of course as designed—12 programs each year. Contact: Ms. Estelle Nelson, UCSF, Rm. 432-A, 400 Parnassus Ave., San Francisco 94143. (415) 666-1445.

ALASKA, MONTANA and IDAHO

This list of continuing education programs in Alaska, Montana and Idaho is supplied by the University of Washington School of Medicine's program of regional medical education in Washington, Alaska, Montana and Idaho (WAMI). To have events listed, please send information to: WAMI Program, CME Calendar, D-207 Health Sciences Building, School of Medicine, SC-64, University of Washington, Seattle, Washington 98195; or phone (206) 543-6995.

ALASKA

May 27—**Univ. of Wash. Ob/Gyn Session** (Anchorage). Wednesday, 12-1 p.m. Providence Hospital. Contact: Hedric Hanson, MD, 3300 Providence Drive, Anchorage, AK 99504. (907) 276-8385.

June 18—**Consultation on Adolescent Problems/Systems Approach—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday, 7:30 pm-9:30 pm. Alaska Psychiatric Institute Medical Library. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99503. (907) 274-7579.

MONTANA

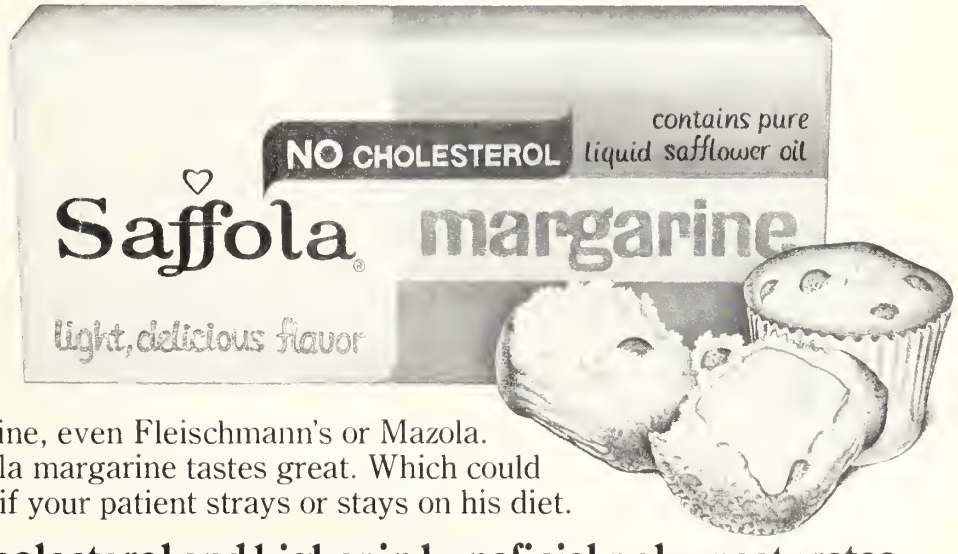
May 27-29—**Office Endocrinology—Univ. of Wash. Internal Medicine Review Sessions.**

Cheer up a low cholesterol diet with Saffola.

Saffola margarine is perfect for your patients following a low-cholesterol diet.

Not just because Saffola has no cholesterol. And is higher in beneficial polyunsaturates than corn oil margarine, even Fleischmann's or Mazola.

But because Saffola margarine tastes great. Which could mean the difference if your patient strays or stays on his diet.



Absolutely no cholesterol and higher in beneficial polyunsaturates.

May 27, Wednesday, Great Falls. 5-7:30 p.m. Columbus Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

May 28, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: D. Frank Johnson, MD, Marillac Hall, Billings, MT 59101. (406) 657-7083.

May 29, Friday, Missoula. 8-10:30 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

June 10—**Allergy—Univ. of Wash. Pediatrics Sessions** (Great Falls). Wednesday. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

IDAHO

May 18—**Evaluation and Treatment of Premature Labor—Univ. of Wash. Ob/Gyn Sessions** (Boise). Monday. 12-1 p.m., St. Luke's Hospital. Contact: David M. Barton, MD, 999 N. Curtis Rd., Boise, ID 83706. (208) 385-9391.

May 19—**Psychiatry—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12-1 p.m., St. Anthony Hospital. Contact: David Fischel, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

NEW MEXICO

All courses listed below have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. The Continuing Medical Education Committee of the New Mexico Medical Society has certified all courses listed below as meeting the criteria for Category 4 under the New Mexico Board of Medical Examiners Continuing Medical Education regulations.

Information and requests for accreditation should be sent to the chairman of the CME Committee, New Mexico Medical Society, P.O. Box 9366, Albuquerque, NM 87119 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 247-0539.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

May 15—**New Techniques in Diagnostic Imaging and Radiotherapy.** Albuquerque. Friday. Four Seasons Motor Inn. 4 credit hours. Contact: CME Office, UNM School of Medicine, Albuquerque, NM 87131. (505) 277-3942.

May 15-16—**Pediatric Cardio-Pulmonary Update Symposium.** Albuquerque. Friday-Saturday. Convention Center. 10 credit hours. Contact: Steven Yabek, MD, Dept. of Pediatrics, UNM School of Medicine, Albuquerque, NM 87131. (505) 277-4361.

June 25-27—**Oxygen Transport to Human Tissues—A Symposium in Honor of Dr. U. C. Luft.** Albuquerque. Thursday-Saturday. Lovelace Medical Center. 16.5 credit hours. Contact: Waneta C. Tuttle, PhD, Lovelace Medical Foundation, 5400 Gibson SE, Albuquerque, NM 87108. (505) 832-7155.

July 20-23—**Ruidoso Family Practice Seminar.** Ruidoso. Monday-Thursday. Inn of the Mountain Gods. 18 credit hours, also AAFP Prescribed. Contact: Convention Director, PO Box 456, Sunland Park, NM 88063. (505) 247-0539.

Classified Advertisements

USE THIS ORDER BLANK TO ADVERTISE PHYSICIAN OPPORTUNITIES, SITUATIONS WANTED, PRACTICES, OFFICES, MEDICAL EQUIPMENT, ETC.

CLOSING DATE for copy and advance payment: 5th of month PRECEDING date of issue.

The rate for each insertion is **$4.00 per line** (average six words per line) **with five line minimum.**
DISPLAY RATES. $40.00 per inch.
Box number charge: $2.00 each month.

CLASSIFIED ADVERTISEMENTS ARE PAYABLE IN ADVANCE. PLEASE TYPE OR PRINT AD COPY.

THE WESTERN Journal of Medicine 731 MARKET ST. • SAN FRANCISCO, CA 94103 • TEL. (415) 777-2000, EX. 220

_____

_____

_____

_____

_____

Name _____ Address _____

Enclosed is $_____ for _____ (No. Mos.) insertion(s).

Check one: ☐ Please include my name and address in ad
☐ Please assign a box number ($2.00 additional for each month's insertion)

July 22-25—**Current Concepts in the Surgical Pathology of the Thyroid, Parathyroid, Thymus and Mediastinum.** Santa Fe. Wednesday-Saturday. Santa Fe Hilton. 15 credit hours. Contact: Symposia de Santa Fe, 465 St. Michaels Dr., Santa Fe, NM 87501. (505) 982-1911.

August 5-8—**Radiology for FP's—An Update.** Santa Fe. Wednesday-Saturday. Santa Fe Hilton Inn. 16 credit hours, also AAFP Prescribed. Contact: W. J. Levy, MD, Symposia de Santa Fe, PO Box 5175, Santa Fe, NM 87502.

September 3-5—**Sports Medicine.** Albuquerque. Thursday-Saturday. Location to be announced. 10 credit hours. Contact: Otto Appenzeller, MD, Dept. of Neurology, UNM School of Medicine, Albuquerque, NM 87131. (505) 277-3342.

September 27-October 1—**Southwest Obstetrical & Gynecological Society 1981 Annual Meeting.** Santa Fe. Sunday-Thursday. Inn at Loretto. 30 credit hours, also AAFP Prescribed. Contact: W. Duane McCarty, MD, 5400 Gibson SE, Albuquerque, NM 87108. (505) 842-7291.

OREGON

This bulletin of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

University of Oregon Medical School, Department of Psychiatry, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, University of Oregon Medical School. Contact: Dept. of Psychiatry, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8144.

University of Oregon Medical School, Department of Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, University of Oregon Medical School. Contact: Dept. of Medicine, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8607.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, OR 97213. (503) 234-8211.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00-9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee, P.O. Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

EMERGENCY MEDICINE

June 4-6—**Update: Emergency Medicine.** Sponsored by the Oregon Chapter of ACEP, EDNA and OSEMTA. Thursday-Saturday. Salishan Lodge, Gleneden Beach, Oregon. For additional information please contact: Vivian Curry, c/o E/PCP Program, Good Samaritan Hospital & Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7711.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center, Portland. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-7590.

OBSTETRICS AND GYNECOLOGY

October 1-3—**Pacific Northwest Review of Obstetrics & Gynecology.** Thursday-Saturday. Thunderbird-Jantzen Beach, Portland, Oregon. For additional information please contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, Portland, OR 97201. (503) 226-1555.

INTEREST TO ALL PHYSICIANS

September 11-12—**Ashland Conference: Gastroenterology.** Friday-Saturday. Ashland Hills Inn, Ashland, Oregon. For additional information please contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, Portland, OR 97201. (503) 226-1555.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. Please send information to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle 98121; or phone (206) 623-4801.

May 18—**Arrhythmias—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, PO Box 489, Wenatchee, WA 98801. (509) 663-8711.

May 19—**Evaluation and Treatment of Premature Labor—Univ. of Wash. OB/GYN Sessions.** (Spokane). Tuesday. 12-1 p.m., Sacred Heart Medical Center. Contact: Wm. Harvey Frazier, MD, West 101 8th Ave., Spokane, WA 99204. (509) 838-8347.

May 22-23—**Northwest Academy of Otolaryngology and Head and Neck Surgery Annual Scientific Program.** Seattle. Friday-Saturday. Washington Athletic Club. Contact: C. Thomas Yarington, MD, The Mason Clinic, 1100 Ninth Avenue, Seattle, WA 98101. (206) 223-6833.

May 22-24—**Comprehensive Care for Physically Disabled Children.** Seattle. Friday-Sunday. Washington Plaza. Contact: John A. Hinckley, AACPDM, PO Box 11083, Richmond, VA 23230. (804) 355-0147.

May 23-30—**Allergy and Immunology.** Maui, Hawaii. Saturday-Saturday. U/W at Wailea Beach, Maui, Hawaii. Contact: U/W School of Medicine.

May 29-30—**Northwest Association of Physical Medicine and Rehabilitation.** Friday-Saturday. Seattle. Washington Plaza Hotel. Contact: Eugen Halar, MD, Seattle VA Medical Center, RMS (117), 4435 Beacon Avenue South, Seattle, WA 98108. (206) 762-1010, Ext. 138.

June 4-5—**Pacific Northwest Chapter of the American College of Chest Physicians: Cardiopulmonary Symposium.** Seattle. Thursday-Friday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

June 9—**Pediatric Allergy—Univ. of Wash. Pediatrics Sessions** (Spokane). Tuesday. 12-1 p.m., Sacred Heart Medical Center. Contact: Frank Reynolds, MD, WAMI Office, 3 North, Sacred Heart Medical Center, Spokane, WA 99204. (509) 455-8220.

June 11-12—**Regional Anesthesia and Nerve Block.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

June 15—**Antibiotic Update.** Sacred Heart Medical Center. Spokane. Monday. Contact: U/W School of Medicine.

June 15-19—**Death Investigation.** Seattle. Monday-Friday. Contact: U/W School of Medicine.

June 16—**Antibiotic Update.** U/W Health Sciences Building. Seattle. Tuesday. Contact: U/W School of Medicine.

June 18-19—**Respiratory Care.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

June 18-20—**Modern Office Procedures: Minor Surgeries.** Seattle. Thursday-Saturday. Contact: U/W School of Medicine.

June 22—**Ophthalmology for the Internist—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

July 19-27—**Alaska Cruise: OB/GYN.** Sunday-Monday. Contact: U/W School of Medicine.

July 24-26—**Washington State Society of Anesthesiologists: Seafair III Anesthesia Meeting.** Seattle. Friday-Sunday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

July 27-31—**Psychiatry & The Behavioral Sciences: The 1980s.** Bayshore Inn. Vancouver, British Columbia. Monday-Wednesday and Friday. Contact: U/W School of Medicine.

August 5-7—**Great Debates in Otolaryngology.** Seattle. Wednesday-Friday. Contact: U/W School of Medicine.

August 21-28—**Alaska Cruise: Radiology.** Friday-Friday. Contact: U/W School of Medicine.

August 21-28—**Alaska Cruise: Strabismus.** Friday-Friday. Contact: U/W School of Medicine.

COURSE SPONSORS AND CONTACT INFORMATION

CME PIERCE COUNTY—Contact: Mrs. Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON) — Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Sandra McDonald, Division of Continuing Medical Education, Virginia Mason Medical Center, 1100 Ninth Avenue, Seattle, WA 98101. (206) 223-6898.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the Academy for Continuing Medical Education, a foundation of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Academy for Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the Academy at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the Academy for current details.

GRAND ROUNDS

SPONSOR: Primary Children's Medical Center
TITLE: **Pediatric Grand Rounds**
LOCATION: PCMC
DATE: First and third Thursdays—8:00 a.m.
CONTACT: Cathy Van Komen (801) 363-1221
SPONSOR: Utah Valley Hospital, Provo
TITLE: **Interdepartmental Grand Rounds**
LOCATION: UVH
CONTACT: Gary Watts, MD (801) 373-7850 (Ext. 2143)

* * *

May 18-23

SPONSOR: University of Utah
TITLE: **Training and Certification of Pulmonary Function Testing**
LOCATION: University Medical Center
FEE: To be announced
CREDIT: To be announced
CONTACT: Katharine Blosch (801) 581-5710

SPONSORS OF COURSES—ABBREVIATIONS

AF: Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.
CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.
CWH: Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461
FHP: Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.
HAFB: Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.
HCH: Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.
LDSH: Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.
MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.
OEH: Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.
OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409
PCMC: Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.
SHCC: Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.
SLSC: Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.
UAFP: Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.
UUMC: University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.
UVH: Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.
VAMC: Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

May 22-23

SPONSOR: University of Utah
TITLE: **Advanced Trauma Life Support**
LOCATION: Tri-Arc Travelodge, Salt Lake City
FEE: $300.00
CREDIT: 17 hours
CONTACT: Tricia Neilson, RN (801) 533-6435

June 3-6

SPONSOR: University of Utah
TITLE: **7th Boston Lacrimal Course**
LOCATION: Holiday Inn, Park City
FEE: To be announced
CREDIT: 20 hours
CONTACT: Darrell E. Wolfley, MD (801) 363-3355

June 11-12

SPONSOR: Castleview Hospital
TITLE: **5th Annual Castle Country Symposium** (with Rock Art Jeep Safari—6-13)
LOCATION: Price
FEE: $75.00
CREDIT: 12 hours
CONTACT: Mary Louise Ghirardelli (801) 637-4800

June 17-19

SPONSOR: University of Utah
TITLE: **Society for Epidemiologic Research**
LOCATION: Snowbird
FEE: To be announced
CREDIT: 22.5 hours
CONTACT: Joseph L. Lyon, MD (801) 581-5270

June 22-25

SPONSOR: University of Utah
TITLE: **Alcoholism and Other Drug Dependencies**
LOCATION: University Medical Center, Classroom C
FEE: To be announced
CREDIT: 25 hours
CONTACT: James R. Swenson, MD (801) 581-7985

June 30-July 3

SPONSOR: University of Utah
TITLE: **8th Annual Symposium in Clinical Echocardiography: New Developments in Cardiac Ultrasound**
LOCATION: Snowbird
FEE: To be announced
CREDIT: 23.5 hours
CONTACT: A. D. Hagan, MD (801) 350-1680

July 31-August 6

SPONSOR: University of Utah
TITLE: **Radiology 3rd Annual Postgraduate Course**
LOCATION: Inside Passage, Alaska
FEE: $300.00
CREDIT: 28 hours
CONTACT: Ann Osborn, MD (801) 581-7552

September 3-5

SPONSOR: University of Utah
TITLE: **Advanced Trauma Life Support**
LOCATION: Tri-Arc Travelodge, Salt Lake City
FEE: $300.00
CREDIT: 17 hours
CONTACT: Tricia Neilson, RN (801) 533-6435

September 9-11

SPONSOR: University of Utah/Utah State Medical Association
TITLE: **Annual Scientific Session**
LOCATION: Hotel Utah, Salt Lake City
FEE: $50.00
CREDIT: 12 hours
CONTACT: Maxcine Fry (801) 355-7477

Pacific Heights is beneath us.

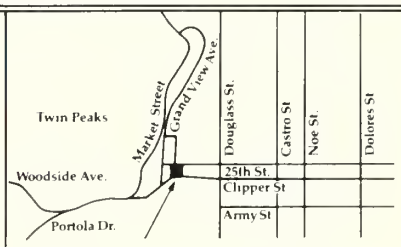
Grand View Terrace puts you at the top in San Francisco. These contemporary town house condominiums offer a standard of luxury befitting their high position.

First, they're wonderfully spacious and airy, with bay windows that command a magnificent panoramic view of the entire Bay Area. And each home has over-sized rooms with 9 foot ceilings, extra wide hallways, wood burning fireplaces, skylights, individual dressing rooms, large closets, redwood decks and a one or two car garage. Some have garden atriums.

Below market financing available.

Come see it all. The grand view, luxurious interiors and the spacious quality that comes from living near the top of Twin Peaks in San Francisco.

Prices range from $265,000 to $325,000. Model home open



daily from 1 to 5 pm, 7 days a week, 760 Clipper Street.

Grand View Terrace
Clipper and Grand View Streets
San Francisco, CA 94114
(415) 641-0601

©1981 Grand View Development Corporation, Builders

WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—4107 Laurel St., Anchorage 99504. Annual Meeting: May 23-27, 1981, Glacier Bay Lodge, Glacier Bay.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. Annual Meeting: May 20-24, 1981, The Pointe Resort, Phoenix.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: March 12-17, 1982, Disneyland Hotel, Anaheim.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. Annual Meeting: September 9-12, 1981, Keystone.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. Annual Meeting: October 12-16, 1981, Ilikai Hotel, Honolulu.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. Annual Meeting: July 23-26, 1981, Sun Valley.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Annual Meeting: October 1-3, 1981, Copper King Inn, Butte.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. Annual Meeting: May 15-17, 1981, Carson City.

New Mexico Medical Society—2650 Yale SE, Albuquerque 87106. Annual Meeting: May 6-8, 1981, Hilton Inn, Albuquerque.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. Annual Scientific Session: October 29-30, 1981, Portland.

Utah State Medical Association—540 East Fifth South, Salt Lake City 84102. Annual Meeting: September 8-11, 1981, Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. Annual Meeting: September 24-27, 1981, Davenport Hotel, Spokane.

Wyoming State Medical Society—P.O. Drawer 4009, Cheyenne 82001. Annual Meeting: June 22-26, 1981, Americana Snow King Hotel, Jackson.

October 9

SPONSOR: University of Utah
TITLE: **Regional Joint ACP-ASIM Meeting Topics in Pharmacology**
LOCATION: Salt Lake Hilton
FEE: $20.00
CREDIT: To be announced
CONTACT: Gregory A. Schwitzer, MD (801) 581-7818

October 16-27

SPONSOR: Washington University School of Medicine/ Utah State Medical Association
TITLE: **Western Mediterranean Air/Sea Cruise and Medical Seminar**
LOCATION: Portugal, Morocco, Gilbraltar, Spain, Italy, France
FEE: $250.00 (medical seminar registration only)
CREDIT: 27 hours
CONTACT: Maxcine Fry (801) 355-7477

November 6

SPONSOR: LDS Hospital
TITLE: **Postgraduate Course—Renal/Pulmonary Syndromes**
LOCATION: Hotel Utah, Salt Lake City
FEE: To be announced
CREDIT: To be announced
CONTACT: C. DuWayne Schmidt, MD (801) 350-1813

November 13-14

SPONSOR: University of Utah
TITLE: **Advanced Trauma Life Support**
LOCATION: Tri-Arc Travelodge, Salt Lake City
FEE: $300.00
CREDIT: 17 hours
CONTACT: Tricia Neilson, RN (801) 533-6435

January 16-20, 1982

SPONSOR: University of Utah
TITLE: **Immune Consequences of Thermal and Traumatic Injury**
LOCATION: Snowbird
FEE: $200-$225
CREDIT: 19 hours
CONTACT: John L. Ninnemann, PhD (801) 581-7617

Note: Dates, times, places and programs are subject to change on occasion. Please check with the sponsoring organization or the Academy for details.

Index to

The Western Journal of Medicine Advertising

AMERICAN MEDICAL ASSOCIATION
Clinical Update Meeting—Hawaii 25
AYERST LABORATORIES
Premarin 20, 21, 22
BANK OF AMERICA
Professional Practice Management 31
BRISTOL LABORATORIES
Tegopen 16, 17
BURROUGHS WELLCOME CO.
Empirin c Codeine 3
Neosporin Topical 33
CLASSIFIED 24, 34, 36, 37
COMP-U-MED SYSTEMS 5
DOCTORS' CO., THE 18
ELI LILLY AND COMPANY
Keflex 15
HEDECO
Entero-Test 6
HOMES OF HERITAGE 45
HOTEL CORPORATION OF HAWAII 2
INSURANCE CORPORATION OF AMERICA 27
KEY PHARMACEUTICALS, INC.
Theo-Dur 28, 29, 30
MAUI ELDORADO RESORT 14
NATIONAL KIDNEY FOUNDATION OF NORTHERN CALIFORNIA
14th Annual Symposium on Renal Disease 30
NORCAL MUTUAL INSURANCE CO. 38
PVO INTERNATIONAL
Saffola Margarine 41
ROCHE LABORATORIES
Bactrim ..... 2nd Cover, 1, 2
Limbitrol ..... 3rd and 4th Covers
SMITH KLINE & FRENCH CO.
Dyazide 32
E. R. SQUIBB & SONS INC.
Corgard 8, 9 10
UPJOHN CO., THE
Motrin 12, 13, 14
WESTERN JOURNAL OF MEDICINE, THE
Subscription 35

THE WESTERN Journal of Medicine

VOLUME 134 • NUMBER 6 **JUNE 1981**

477 *Toxic Shock Syndrome* MARTHA H. TANNER, MD; BARBARA J. PIERCE, RN, and DeVON C HALE, MD

485 *Radiologic Errors in Patients With Lung Cancer* JOHN V. FORREST, MD, and PAUL J. FRIEDMAN, MD

491 *Preoperative Management of Proximal Lesions of the Left Coronary Artery System: Surgical Implications*
HANS J. KREBBER, MD; ROBERT J. SZARNICKI, MD, and J. DONALD HILL, MD

NUTRITION IN MEDICINE

496 *Iron Deficiency: Diagnosis and Treatment* PETER R. DALLMAN, MD

SPECIALTY CONFERENCE

506 *Heroin Addiction and Pregnancy*
Moderator: RICHARD A. BASHORE, MD; Discussants: JAMES S. KETCHUM, MD; KLAUS J. STAISCH, MD; CYNTHIA T. BARRETT, MD, and EMERY G. ZIMMERMANN, MD

MEDICAL STAFF CONFERENCE

515 *Diverticular Disease of the Colon* Chief Discussant: JOHN P. CELLO, MD

IMPORTANT ADVANCES IN CLINICAL MEDICINE

524 *Obstetrics and Gynecology—Epitomes of Progress*

EDITORIALS

532 • *Of Gluts and Prices* • *Iron Nutrition* • *Is There Miscommunication About Private Practice?*

CASE REPORTS

535 *Toxic Shock Syndrome in a 19-Year-Old Woman*
MARY RACHEL FARIS, MD; WILLIAM F. SKEEN, MD, MPH, and LISA A. ABRAHAMS, BA

539 *Control of Refractory Ventricular Ectopy—Atrial and Ventricular Overdrive Pacing*
ROY MEYER, MD, and LESTER B. JACOBSON, MD

CORRESPONDENCE

545 • *Malaria in California* • *Still More HAFE* • *Diagnosis of Human Pulmonary Dirofilariasis* • *Teaching the Pelvic Examination in an Internal Medicine Residency Program* • Ave Atque Vale

SPECIAL ARTICLE

549 *The Halsted Mastectomy: Present Illness and Past History* CORDELIA SHAW BLAND

INFORMATION

Notes on Health Issues for Women

556 *Understanding the Medical and Psychological Aspects of Rape* FRAN PEPITONE-ROCKWELL, PhD

557 *Battered Wives* DONNA M. MOORE, MD

559 *Women in Medicine: Myths and Realities* FRAN PEPITONE-ROCKWELL, PhD, and DON A. ROCKWELL, MD

560 *Incest* SANDRA BAKER, MSW, LCSW

562 *In Memoriam*

564 *Volume Index*

Books Received, See Advertising Page 40

Detailed Table of Contents, See Advertising Pages 7 and 12

Information for Authors, See Advertising Page 26

★ **CONTINUING MEDICAL EDUCATION ACTIVITIES ... CALIFORNIA, HAWAII AND NEVADA; ALASKA, IDAHO; NEW MEXICO; OREGON; WASHINGTO**
(See Advertising Page 19)

★★ **Official Journal of the California Medical Assoc the Idaho Medical Association, the Nevada Stat Association, the New Mexico Medical Society, the Utah State Medical Association and the Washington State Medical Association**

★5115 MA 02115★
BOSTON
10 SHATTUCK STREET
THE NEW ENGLAND JOURNAL
ARNOLD S RELMAN MD EDITOR
11692-021 810602RELMAN**ASC1★

UNPARALLELED PROOF OF NIGHT-LONG EFFICACY

ONLY DALMANE® C IV

flurazepam HCl/Roche

IS SIGNIFICANTLY EFFECTIVE AGAINST THE MAJOR FORMS OF INSOMNIA WITH NO WORSENING OF SLEEP ON DISCONTINUATION

Because subjective reports of insomnia and subsequent experience with sleep medication do not adequately substantiate either the validity of the complaints or the efficacy of medication, the sleep laboratory has become a valuable tool to do both. It is here that Dalmane has been objectively tested and proven effective.

Patients with objectively validated insomnia—difficulty in falling asleep, staying asleep, or both—received Dalmane 30 mg for up to 28 consecutive nights with no increase in dosage and no significant decrease in efficacy. And, upon discontinuation of Dalmane, there was no worsening of sleep past baseline levels on any parameter.[1-3]

Since insomnia is often transient, therapy for as long as 4 weeks should be given only after careful assessment of patient need with special attention to periodic blood counts and liver and kidney function tests.

Advise patients who ingest alcoholic beverages or other CNS depressants against doing so while on Dalmane therapy.

Patients should also be cautioned against engaging in hazardous occupations requiring mental alertness, such as operating machinery or driving a motor vehicle after ingesting the drug.

THE START
within 17 minutes,
rage[4]
THROUGH THE NIGHT
With fewer awakenings[4]
AKENING
7 to 8 hour sleep,
rage[4]
ROCHE®
Please see summary of product information on the following page.

THE STANDARD FOR HYPNOTIC EFFICACY WITH IMPORTANT ADDED BENEFITS

- Well tolerated[4]
- Does not significantly influence the results of many commonly ordered laboratory tests, including triglycerides, uric acid, glucose, SGOT, alkaline phosphatase and total protein[5,6] (See adverse reactions section of complete product information.)
- Compatible with chronic warfarin therapy; no unacceptable fluctuation in prothrombin time reported[7,8]

UNLIKE NONSPECIFIC MEDICATIONS USED FOR SLEEP

Tricyclic antidepressants

–which are *not* sleep specific,[9] yet are sometimes used in nondepressed patients for sleep

–which can cause transient insomnia in the elderly[10]

–which can require careful monitoring in cardiovascular patients[10]

–which have strong anticholinergic effects[10]

Antihistamines

–which are *not* reliable sleep-inducing agents[11]

–which may produce stimulation instead[11]

–which have anticholinergic effects[11]

Major tranquilizers

–whose side effects may be troublesome for nonpsychotic patients[12]

–where tolerance for sedation appears rapidly[12]

Dalmane (flurazepam HCl/Roche) does not cause worsening of sleep beyond baseline levels upon discontinuation.[13]

EFFECTIVE ALL NIGHT SLEEP-SPECIFIC

DALMANE® C IV

flurazepam HCl/Roche

One 15-mg capsule *h.s.*–recommended initial dosage for elderly or debilitated patients.
One 30-mg capsule *h.s.*–usual adult dosage
(15 mg may suffice in some patients).

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; in acute or chronic medical situations requiring restful sleep. Objective sleep laboratory data have shown effectiveness for at least 28 consecutive nights of administration. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended.

Contraindications: Known hypersensitivity to flurazepam HCl.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).

***Usage in Pregnancy:* Several studies of minor tranquilizers (chlordiazepoxide, diazepam, and meprobamate) suggest increased risk of congenital malformations during the first trimester of pregnancy. Dalmane (flurazepam HCl/Roche), a benzodiazepine, has not been studied adequately to determine whether it may be associated with such an increased risk. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated patients, it is recommended that the dosage be limited to 15 mg to reduce risk of oversedation, dizziness, confusion and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies, or with impaired renal or hepatic function. Periodic blood counts and liver and kidney function tests are advised during repeated therapy.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity, and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase.

Dosage: Individualize for maximum beneficial effect.
Adults: 30 mg usual dosage; 15 mg may suffice in some patients.
Elderly or debilitated patients: 15 mg recommended initially until response is determined.

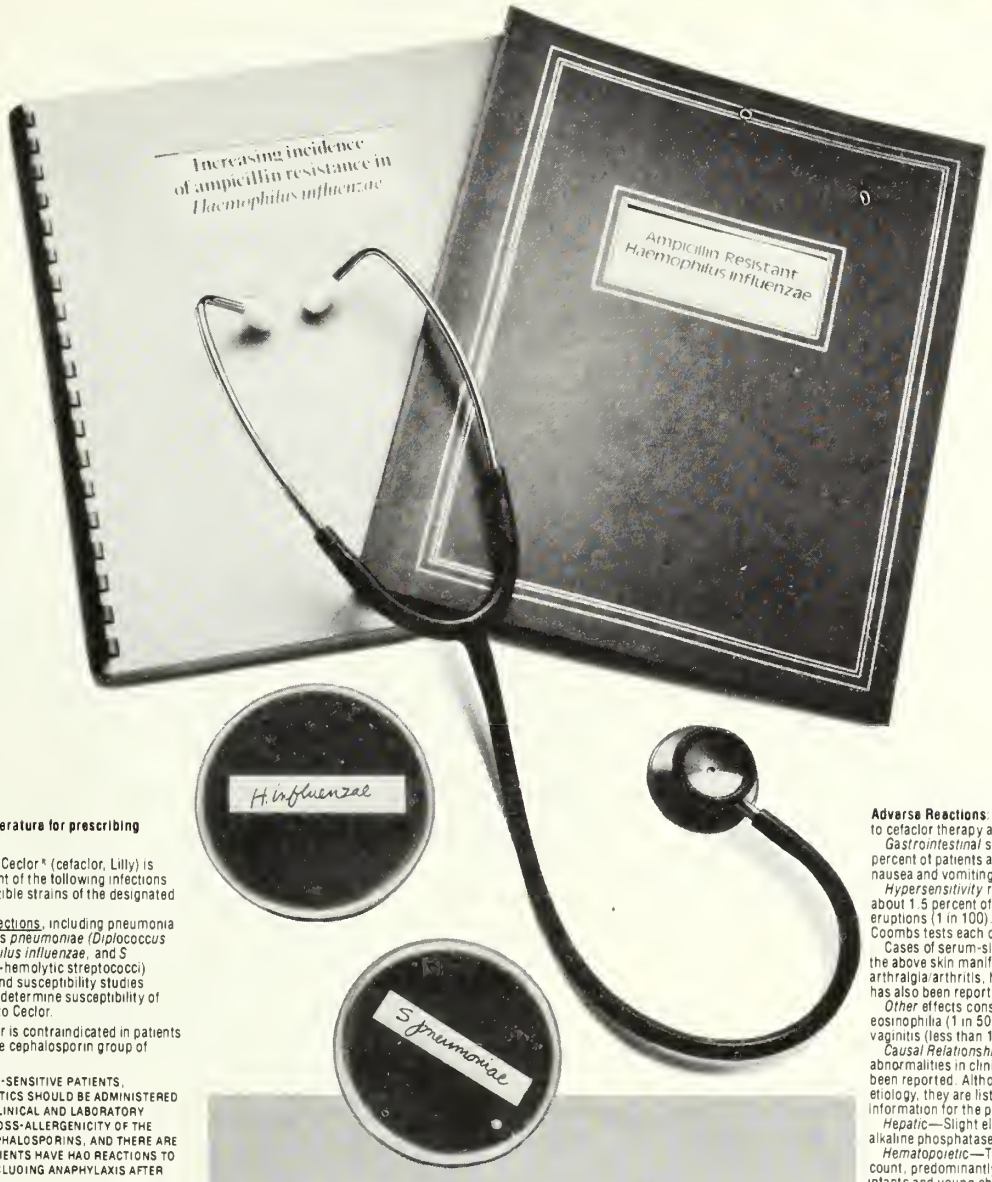
Supplied: Capsules containing 15 mg or 30 mg flurazepam HCl.

ROCHE®

ROCHE PRODUCTS INC.
Manati, Puerto Rico 00701

References: 1. Kales A, *et al: Clin Pharmacol Ther 19*:576-583, May 1976 **2.** Dement WC, *et al: Behav Med 5*:25-31, Oct 1978 **3.** Kales A, *et al: Clin Pharmacol Ther 18*:356-363, Sep 1975 **4.** Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ **5.** Moore JD, Weissman L: *J Clin Pharmacol 16*:241-244, May-Jun 1976 **6.** Spiegel HE: Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ **7.** Robinson DS, Amidon EL: Interaction of benzodiazepines with warfarin in man, in *The Benzodiazepines*, edited by Garattini S, Mussini E, Randall LO. New York, Raven Press, 1973, pp. 641-646 **8.** Warfarin Study: Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ **9.** Baldessarini RJ: Drugs and the treatment of psychiatric disorders, chap. 19, in Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, ed 6. New York, Macmillan Publishing Co. Inc., 1980, pp. 391-447 **10.** Cole JO, Davis JM: Antidepressant drugs, chap. 31.2, in *Comprehensive Textbook of Psychiatry/II*, edited by Freedman AM, Kaplan HI, Sadock BJ, ed 2. Baltimore, The Williams & Wilkins Company, vol 2, 1976, pp. 1941-1956 **11.** Douglas WW: Histamine and 5-hydroxytryptamine (serotonin) and their antagonists, chap. 26, in Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, ed 6. New York, Macmillan Publishing Co. Inc., 1980, pp. 609-646 **12.** Davis JM, Cole JO: Antipsychotic drugs, chap. 31.1, in *Comprehensive Textbook of Psychiatry/II*, edited by Freedman AM, Kaplan HI, Sadock BJ, ed 2. Baltimore, The Williams & Wilkins Company, vol 2, 1976, pp. 1921-1940 **13.** Kales A, *et al: JAMA 241:*1692-1695, Apr 20, 1979

An added complication... in the treatment of bacterial bronchitis*



Some ampicillin-resistant strains of Haemophilus influenzae—a recognized complication of bacterial bronchitis*—are sensitive to treatment with Ceclor.[1-6]

In clinical trials, patients with bacterial bronchitis due to susceptible strains of Streptococcus pneumoniae, H. influenzae, S. pyogenes (group A beta-hemolytic streptococci), or multiple organisms achieved a satisfactory clinical response with Ceclor.[7]

Ceclor®
cefaclor

Pulvules®, 250 and 500 mg

Brief Summary
Consult the package literature for prescribing information.

Indications and Usage: Ceclor® (cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms.

Lower respiratory infections, including pneumonia caused by *Streptococcus pneumoniae (Diplococcus pneumoniae), Haemophilus influenzae,* and *S pyogenes* (group A beta-hemolytic streptococci).

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor.

Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS TO BOTH DRUG CLASSES (INCLUDING ANAPHYLAXIS AFTER PARENTERAL USE).

Antibiotics, including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

Precautions: If an allergic reaction to cefaclor occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids.

Prolonged use of cefaclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs test may be due to the drug.

Ceclor should be administered with caution in the presence of markedly impaired renal function. Under such a condition, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

As a result of administration of Ceclor, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly).

Usage in Pregnancy—Although no teratogenic or antifertility effects were seen in reproduction studies in mice and rats receiving up to 12 times the maximum human dose or in ferrets given three times the maximum human dose, the safety of this drug for use in human pregnancy has not been established. The benefits of the drug in pregnant women should be weighed against a possible risk to the fetus.

Usage in Infancy—Safety of this product for use in infants less than one month of age has not been established.

Adverse Reactions: Adverse effects considered related to cefaclor therapy are uncommon and are listed below:

Gastrointestinal symptoms occur in about 2.5 percent of patients and include diarrhea (1 in 70) and nausea and vomiting (1 in 90).

Hypersensitivity reactions have been reported in about 1.5 percent of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs tests each occur in less than 1 in 200 patients.

Cases of serum-sickness-like reactions, including the above skin manifestations, fever, and arthralgia/arthritis, have been reported. Anaphylaxis has also been reported.

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients).

Causal Relationship Uncertain—Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician.

Hepatic—Slight elevations in SGOT, SGPT, or alkaline phosphatase values (1 in 40).

Hematopoietic—Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40).

Renal—Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200). [1030BOR]

*Many authorities attribute acute infectious exacerbation of chronic bronchitis to either *S. pneumoniae* or *H. influenzae*.[8]

Note: Ceclor® (cefaclor) is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

References

1 Antimicrob. Agents Chemother., *8*:91, 1975.
2 Antimicrob. Agents Chemother., *11*:470, 1977
3 Antimicrob. Agents Chemother., *13*:584, 1978
4 Antimicrob. Agents Chemother., *12*:490, 1977
5 Current Chemotherapy (edited by W. Siegenthaler and R. Luthy), II:880. Washington, D.C.: American Society for Microbiology, 1978.
6 Antimicrob. Agents Chemother., *13*:861, 1978
7 Data on file, Eli Lilly and Company
8 Principles and Practice of Infectious Diseases (edited by G.L. Mandell, R.G. Douglas, Jr., and J.E. Bennett), p. 487. New York: John Wiley & Sons, 1979

Additional information available to the profession on request from Eli Lilly and Company, Indianapolis, Indiana 46285

Lilly

Eli Lilly Industries, Inc.
Carolina, Puerto Rico 00630

100061

THE WESTERN Journal of Medicine

Since 1902 (ISSN 0093-0415)

731 MARKET ST. • SAN FRANCISCO, CA 94103 • TELEPHONE (415) 777-2000

Official Journal of the California Medical Association, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association and the Washington State Medical Association

MALCOLM S. M. WATTS, MD, *Editor*
LLOYD H. SMITH, JR, MD, *Associate Editor*
DAVID GREER, *Managing Editor*
BARBARA T. ROONEY, *Assistant Managing Editor*
VAL BOSMOE, *Editorial Assistant*
MARY JANE MacDWYER, *Copy Editor*
MARY KAY COWANS, *Advertising Production Manager*
KEVIN McKINNEY, *Circulation Coordinator*

editorial communications to DR. WATTS

business communications to MR. GREER

Editorial Board

Chairman of the Board
Malcolm S. M. Watts, San Francisco, Ca

Special Editor for Idaho
E. R. W. Fox, Coeur d'Alene, Id

Special Editor for Nevada
Thomas J. Scully, Reno, Nv

Special Editor for New Mexico
Marcus J. Smith, Santa Fe, NM

Special Editor for Utah
John H. Holbrook, Salt Lake City, Ut

Special Editor for Washington
David Hopkins, Federal Way, Wa

Allergy
Harold S. Novey, Orange, Ca
Abba I. Terr, San Francisco, Ca

Anesthesiology
Ronald L. Katz, Los Angeles, Ca

Cardiac and Thoracic Surgery
John E. Connolly, Irvine, Ca
Albert Starr, Portland, Or

Chest Diseases
Roger K. Larson, Fresno, Ca
Thomas L. Petty, Denver, Co

Dermatology
John H. Epstein, San Francisco, Ca
George F. Odland, Seattle, Wa
Richard B. Stoughton, San Diego, Ca

General and Family Practice
Daniel D. Roberts, Central Point, Or
Harmon E. Holverson, Emmett, Id
Wilfred Snodgrass, Santa Monica, Ca

General Surgery
Fred M. Anderson, Reno, Nv
Daniel T. Cloud, Phoenix, Az
Paul A. Ebert, San Francisco, Ca
Lucius D. Hill, Seattle, Wa
Frank G. Moody, Salt Lake City, Ut

Industrial Medicine and Toxicology
Thomas H. Milby, Berkeley, Ca

Internal Medicine
Robert W. Burroughs, Spokane, Wa
Theodore C. Eickhoff, Denver, Co
Robert L. Hare, Portland, Or
Robert H. Moser, Philadelphia, Pa
George A. Porter, Portland, Or
Helen M. Ranney, San Diego, Ca
David D. Ulmer, Los Angeles, Ca
Edgar Wayburn, San Francisco, Ca
Ralph C. Williams, Jr, Albuquerque, NM

Neurology
Pierre M. Dreyfus, Sacramento, Ca
Philip D. Swanson, Seattle, Wa
W. C. Wiederholt, La Jolla, Ca

Neurosurgery
John R. Green, Phoenix, Az
Arthur A. Ward, Jr, Seattle, Wa
Charles B. Wilson, San Francisco, Ca

Nuclear Medicine
Joseph P. Kriss, Stanford, Ca

Obstetrics and Gynecology
Ralph C. Benson, Portland, Or
Ralph W. Hale, Honolulu, Hi
W. LeRoy Heinrichs, Stanford, Ca
Morton A. Stenchever, Seattle, Wa

Ophthalmology
Robert S. Hepler, Los Angeles, Ca
Bruce E. Spivey, San Francisco, Ca

Orthopedics
Ernest M. Burgess, Seattle, Wa
Duane M. Kline, Jr, Cheyenne, Wy

Otolaryngology
Roger Boles, San Francisco, Ca
Mansfield F. W. Smith, San Jose, Ca

Pathology
Richard L. Kempson, Stanford, Ca

Pediatrics
Louis K. Diamond, San Francisco, Ca
William L. Nyhan, San Diego, Ca
Irving Schulman, Stanford, Ca
Arnold L. Smith, Seattle, Wa

Pharmacology
George N. Aagaard, Seattle, Wa

Physical Medicine and Rehabilitation
Glenn G. Reynolds, San Jose, Ca

Plastic Surgery
Richard P. Jobe, Los Altos, Ca
N. John Wilde, Fresno, Ca

Psychiatry
Carl Eisdorfer, Seattle, Wa
Alan I. Levenson, Tucson, Az
Helen Tausend, Beverly Hills, Ca
Joe Paul Tupin, Sacramento, Ca

Public Health
J. M. Stubblebine, Greenbrae, Ca

Radiology
M. Paul Capp, Tucson, Az
Melvin M. Figley, Seattle, Wa
Marshall Rowen, Orange, Ca

Urology
Richard Middleton, Salt Lake City Ut
Thomas A. Stamey, Stanford Ca

Consulting Editor
Medical Services and Health Care
Paul J. Sanazaro, Berkeley, Ca

POLICY COMMITTEE

BRAD COHN, MD
CHARLES M. HAIR, MD
GLADDEN V. ELLIOTT, MD
SAMUEL HOROWITZ, MD
ROBERT D. BURNETT, MD
THEODORE W. LORING, MD
MALCOLM S. M. WATTS, MD

Advertisements—THE WESTERN JOURNAL OF MEDICINE is published the first week of each month. Advertising copy must be received not later than the first of the month preceding issue. Advertising rates will be sent on request. Acceptance of advertising is contingent upon approval by the Advertising Committee. The journal reserves the right to reject any advertisement.

ADVERTISING SALES REPRESENTATIVES

EAST:
SAUL HORNIK
12 COURT ST.
FREEHOLD, NJ 07728
TEL: (201) 462-8004

MIDWEST:
R. C. JOHNSON & ASSOCIATES
RICHARD C. JOHNSON
547 WEST MELROSE
CHICAGO, IL 60657
TEL: (312) 327-6969

WEST:
MEDIA SERVICES
DARIEN DeLORENZO
LYNNE JEFFES
2612 BELMONT CANYON RD.
BELMONT, CA 94002
TEL. (415) 595-2203
(415) 348-7478

CLASSIFIED:
731 MARKET ST.
SAN FRANCISCO, CA 94103
TEL. (415) 777-2000
(415) 777-0424

Copyright 1981 by the California Medical Association

Owned and Published by the California Medical Association

All material subject to this copyright appearing in THE WESTERN JOURNAL OF MEDICINE may be photocopied for the noncommercial purpose of scientific or educational advancement. Volumes begin with January and July.

The subscription price per year is $10 in the United States and Canada; $18 in all other countries. Single copies are $2. Address all subscription communications to THE WESTERN JOURNAL OF MEDICINE Circulation, 731 Market St., San Francisco, CA 94103.

Allow six weeks for subscriptions to begin. Past issues must be bought individually. So long as reserve stocks are available, missing issue requests from subscribers are honored for up to six months after the issue date. Thereafter, the single copy rate of $2.00 is applicable for each issue available.

Change of Address—Requests for change of address should give both the old and new addresses. Allow six weeks for change-over.

CONTRIBUTIONS OF SCIENTIFIC AND ORIGINAL ARTICLES

Responsibilities for Statements and Conclusions in Original Articles—Authors are responsible for all statements, conclusions and methods of presenting their subjects. These may or may not be in harmony with the views of the editorial staff. It is aimed to permit authors to have as wide latitude as the general policy of the journal and the demands on its space may permit. The right to reduce, revise or reject any manuscript is always reserved.

Exclusive Publication—Articles are accepted for publication on condition that they are contributed solely to this journal. Ordinarily contributors will be notified within 60 days if a manuscript is accepted for publication. Every effort will be made to return unused manuscripts.

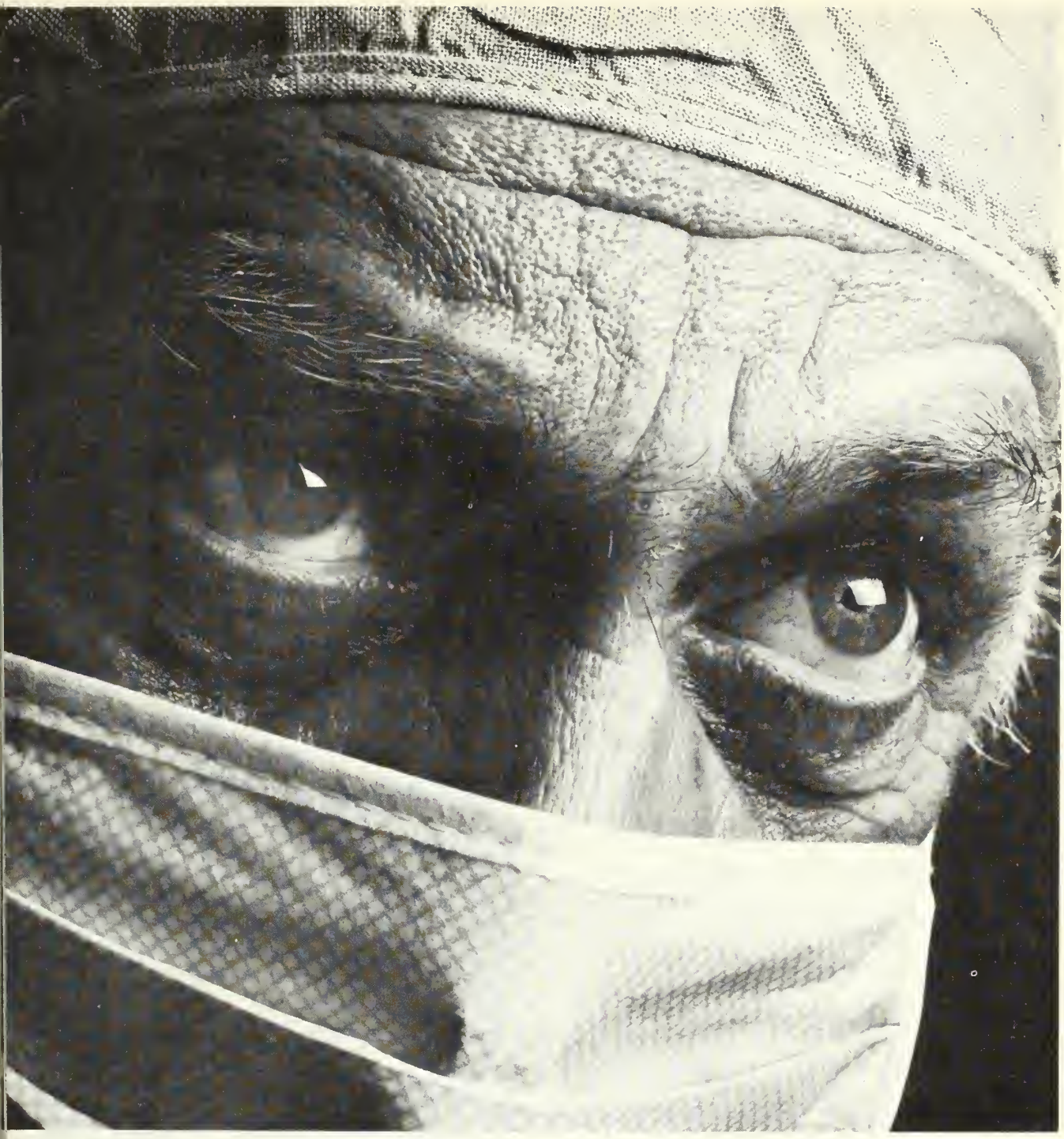
"Information for Authors"—A complete guide to manuscript submission and journal style is available on request and also appears in each January and July issue.

Manuscripts—Ordinarily manuscripts should not exceed 3,000 words (less than 15 typed double-spaced pages). The *original* manuscript and two copies should be submitted, typed double-spaced throughout. If photographic illustrations are desired, three sets of clear, unmounted black and white glossy prints should be supplied. For line drawings, original artwork or glossy prints are acceptable. Tables should be typed on separate sheets of paper.

References—References should conform to the following order: name of author, title of article, name of periodical, and volume with inclusive pages, month and year—i.e., Lee GS: The heart rhythm following therapy with digitalis—In theory and practice. Arch Int Med 44:554-562, Dec 1942. They should be listed in the order in which they are cited in the text, numbered in sequence and punctuated as above.

Reprints—Reprints are available to authors at established standard rates.

"Entered as second class matter at the post office in San Francisco under the Act of March 3, 1879." Acceptable for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized August 10, 1918. Publication Number 084480.



Commitment.

It is evident in a doctor's every action. Commitment. It is the key to professional excellence. In the medical field. And in ours.

At Insurance Corporation of America our commitment has always been to a single goal: To provide physicians with the finest professional liability insurance.

Over the years ICA has consistently offered the strongest possible coverage combined with the highest standard of professional service. Our specialization, conservative management, and commitment in this one field have enabled us to achieve excellence within the industry.

For further information, contact: Insurance Corporation of America, ICA Center 4295 San Felipe, Box 56308, Houston, Texas 77027. 1-800-231-2615. In Texas call 1-800-392-9702 (Check for availability in your state.)

ICA PROFESSIONAL LIABILITY INSURANCE.

WE'RE THE SPECIALIST IN THE FIELD.

Practice what we teach.

Today there are over 31 million men, women and children suffering from the many forms of arthritis and related rheumatic diseases. And there just aren't enough trained rheumatologists to help them.

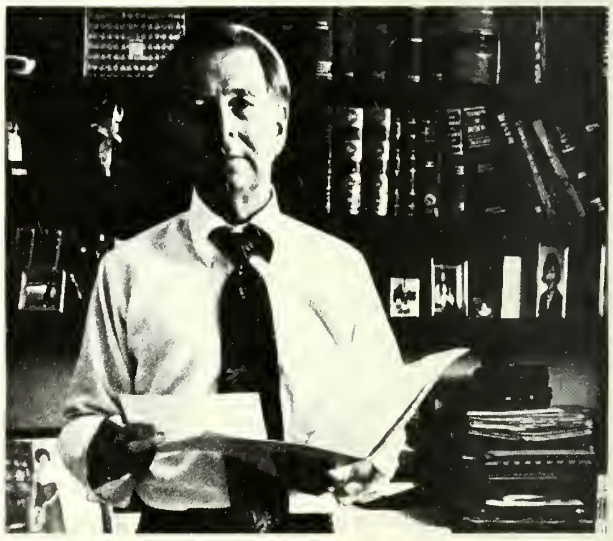
That's why arthritis sufferers need your help.

They must depend heavily on the family practitioner for better diagnosis, more effective patient treatment.

Contact your local Arthritis Foundation chapter for the latest information on arthritis. This includes continuing educational seminars by leading rheumatologists, scientific meetings, "outreach" programs—as well as the "Bulletin on the Rheumatic Diseases," "Arthritis and Rheumatism Journal," "Primer on the Rheumatic Diseases," audio cassettes and other professional materials. Free disease handbooks and medication pamphlets are also available to patients.

Please. Let us help your practice with what we teach.

The Arthritis Foundation helps doctors help.



ARTHRITIS FOUNDATION

A public service of this magazine

THE WESTERN
Journal of Medicine

VOLUME 134 • NUMBER 6 **JUNE 1981**

TABLE OF CONTENTS

477 *Toxic Shock Syndrome* MARTHA H. TANNER, MD; BARBARA J. PIERCE, RN, and DeVON C HALE, MD
From the Department of Infectious Disease, Riverview Hospital, Idaho Falls, Idaho.

485 *Radiologic Errors in Patients With Lung Cancer* JOHN V. FORREST, MD, and PAUL J. FRIEDMAN, MD
From the Department of Radiology, University of California, San Diego, School of Medicine.

491 *Preoperative Management of Proximal Lesions of the Left Coronary Artery System: Surgical Implications*
HANS J. KREBBER, MD; ROBERT J. SZARNICKI, MD, and J. DONALD HILL, MD
From the Department of Cardiovascular Surgery, Pacific Medical Center, San Francisco.

NUTRITION IN MEDICINE

496 *Iron Deficiency: Diagnosis and Treatment* PETER R. DALLMAN, MD
From the Department of Pediatrics, University of California, San Francisco.

SPECIALTY CONFERENCE

506 *Heroin Addiction and Pregnancy*
Moderator: RICHARD A. BASHORE, MD; Discussants: JAMES S. KETCHUM, MD; KLAUS J. STAISCH, MD; CYNTHIA T. BARRETT, MD, and EMERY G. ZIMMERMANN, MD
An edited transcription of an Interdepartmental Conference arranged by the Department of Medicine, UCLA School of Medicine, Center for the Health Sciences, Los Angeles.

MEDICAL STAFF CONFERENCE

515 *Diverticular Disease of the Colon* Chief Discussant: JOHN P. CELLO, MD
A discussion selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from a transcription, it was prepared by Drs. David W. Martin, Jr, Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine.

IMPORTANT ADVANCES IN CLINICAL MEDICINE

Obstetrics and Gynecology—Epitomes of Progress
Items of progress in obstetrics and gynecology. Each item in the judgment of a panel of knowledgeable physicians has recently become reasonably firmly established, both as to scientific fact and important clinical significance.

524 *The Prolactinoma Problem: Long-Term Issues and Short-Term Answers* ERNEST M. GOLD, MD

525 *Prenatal Diagnosis of Short-Limbed Dwarfism by Ultrasonography* ROY A. FILLY, MD

525 *Intrauterine Growth Retardation* ROBERT RESNIK, MD

526 *Recent Advances in Prenatal Diagnosis of Genetic Defects* MITCHELL S. GOLBUS, MD

526 *The Value of Microsurgery in Tubal Repair* CARL J. LEVINSON, MD

527 *Antiprostaglandin Compounds in the Management of Primary Dysmenorrhea*
FREDERICK W. HANSON, MD

527 *A New and Effective Treatment of Hirsutism* S. S. C. YEN, MD

528 *Severe Cardiovascular Complications Associated with β-Sympathomimetic Tocolysis and Their Prevention*
MICHAEL KATZ, MD

529 *Chlamydial Infections in Obstetrics and Gynecology* RICHARD L. SWEET, MD

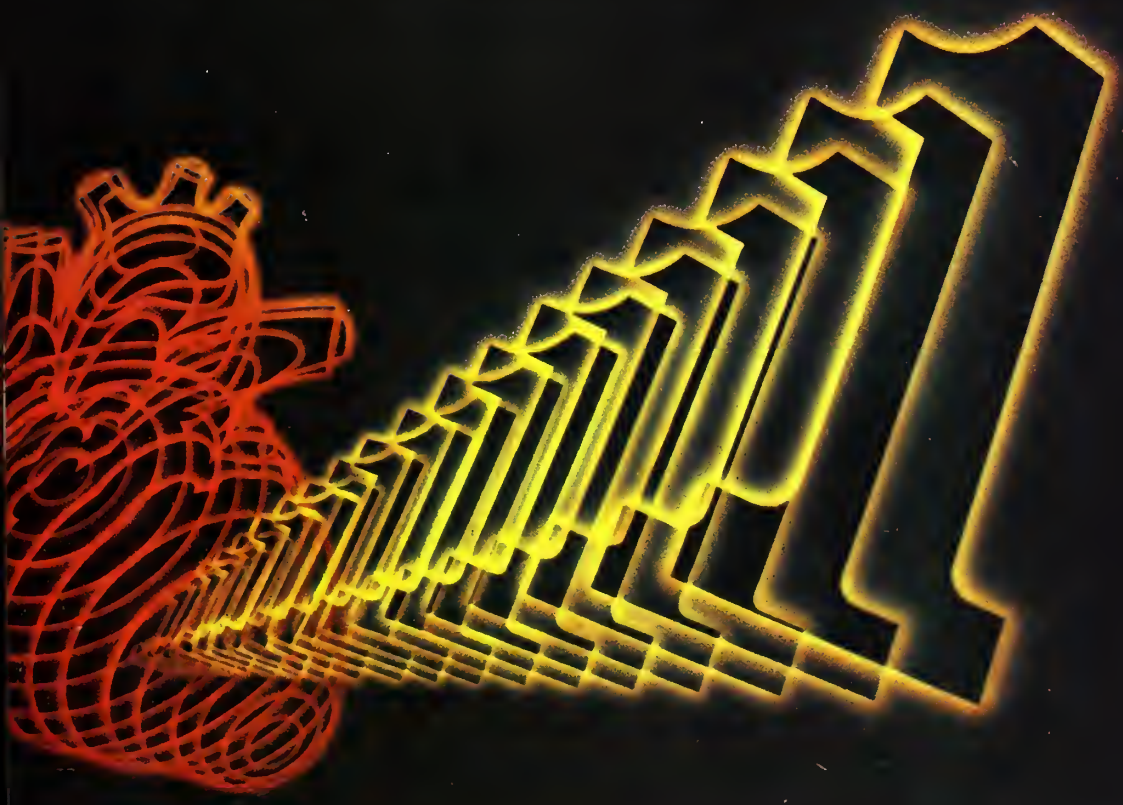
529 *Ovarian Carcinoma: In Vitro Testing of Sensitivity to Chemotherapy* SAMUEL C. BALLON, MD

530 *Two Mechanisms of Late Decelerations: Reflex and Myocardial Hypoxia* J. T. PARER, MD

(Continued on Page 12)

Only one beta-blocker provides once-a-day round-the-clock protection in both hypertension and angina pectoris.

CORGARD®
[nadolol tablets]
IS THE ONE



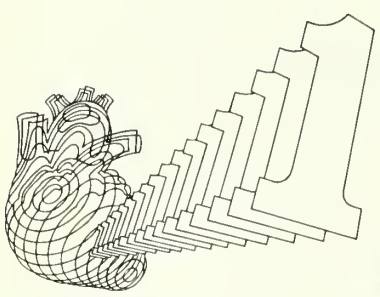
Reliable 24-hour beta blockade at all titrated dosages

SQUIBB®

Innovators in cardiovascular medicine

See next page for brief summary.

The only once-a-day beta-blocker for both hypertension and angina pectoris



CORGARD®
nadolol tablets

40 mg, 80 mg, 120 mg, 160 mg scored tablets

CORGARD® TABLETS
Nadolol Tablets

DESCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery — Because beta-blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute occur commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** — Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory** — Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** — Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System** — reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal** — mesenteric arterial thrombosis; ischemic colitis. **Hematologic** — agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic** — fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous** — reversible alopecia; Peyronie's disease; erythematous rash.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm — Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to 160 mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval — see package insert for dosage in these patients.

For full prescribing information, consult package insert.

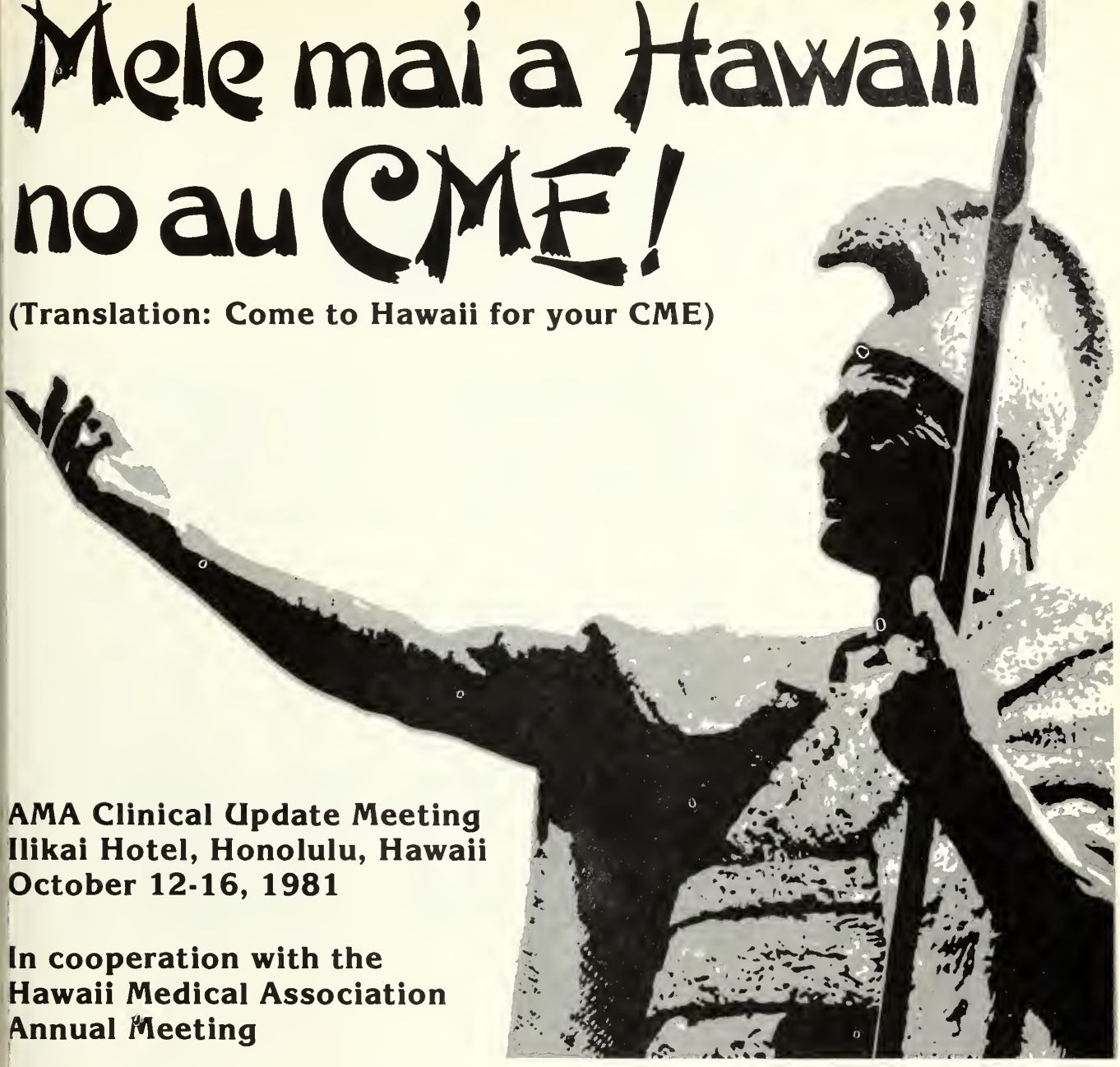
HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and 1000 tablets and in Unimatic® single-dose packs of 100 tablets.

SQUIBB

©1981 E.R. Squibb & Sons, Inc. Issued: March 1981 511-518

Mele mai a Hawaii no au CME!

(Translation: Come to Hawaii for your CME)



AMA Clinical Update Meeting
Ilikai Hotel, Honolulu, Hawaii
October 12-16, 1981

In cooperation with the Hawaii Medical Association Annual Meeting

Thirty 5-hour Postgraduate Courses, Monday-Friday
Choose from 30 Category 1 courses in such specialty areas as cardiology, internal medicine, family medicine, general surgery, pharmacology, pediatrics and gynecology. Substantial syllabi accompany these courses.

Post Meeting Tour to Maui!
Three nights, four days (Saturday-Tuesday, October 17-20) at the Intercontinental Hotel on beautiful, unspoiled Maui. To save on the inter-island portion of the trip, buy your ticket from continental cities to Honolulu and Maui.

Buy Your Plane Tickets Early!
Air fares are increasing rapidly, so obtain your tickets early to get the lowest possible fare.

Plan NOW for Your Trip to Hawaii!
You can surf, golf, go sight-seeing and deep-sea fishing or just relax and let the sun and gentle Tradewinds work their wonders.

Return this coupon for complete information!

Department of Meeting Services
American Medical Association
535 North Dearborn Street WJ
Chicago, Illinois 60610

Please send me information on the AMA Update Meeting in Hawaii, October 12-16, 1981.

Please Print

Name _____

Address _____

City/State/Zip _____

(Continued from Page 7)

EDITORIALS

532 *Of Gluts and Prices*

532 *Iron Nutrition* CLEMENT A. FINCH, MD
Dr. Finch is Professor and Head of the Division of Hematology, University of Washington School of Medicine, Seattle.

533 *Is There Miscommunication About Private Practice?*

CASE REPORTS

535 *Toxic Shock Syndrome in a 19-Year-Old Woman*
MARY RACHEL FARIS, MD; WILLIAM F. SKEEN, MD, MPH, and LISA A. ABRAHAMS, BA
From St. Mary's Hospital and Medical Center, San Francisco.

539 *Control of Refractory Ventricular Ectopy—Atrial and Ventricular Overdrive Pacing*
ROY MEYER, MD, and LESTER B. JACOBSON, MD
From the Division of Cardiology, Presbyterian Hospital of Pacific Medical Center, San Francisco.

CORRESPONDENCE

Malaria in California

545 ERIC L. STIRLING, MD, and THOMAS ROWSELL, MD

545 CHARLES J. BERLETTI, MD

546 *Still More HAFE* CHARLES R. McELROY, MD, and JEROME R. HOFFMAN, MD

547 *Diagnosis of Human Pulmonary Dirofilariasis* FLAVIO CIFERRI, MD, MPH

547 *Teaching the Pelvic Examination in an Internal Medicine Residency Program*
STEPHEN HAMBURGER, MD; DEBORAH GUTHRIE, MA; P. GAIL SMITH, and KITT SHAFFER

548 Ave Atque Vale GEORGE X. TRIMBLE, MD

SPECIAL ARTICLE

549 *The Halsted Mastectomy: Present Illness and Past History* CORDELIA SHAW BLAND
The author is an editor at the UCLA School of Medicine, Center for the Health Sciences, Los Angeles, and a free-lance writer.

INFORMATION

Notes on Health Issues for Women

556 *Understanding the Medical and Psychological Aspects of Rape* FRAN PEPITONE-ROCKWELL, PhD

557 *Battered Wives* DONNA M. MOORE, MD

559 *Women in Medicine: Myths and Realities* FRAN PEPITONE-ROCKWELL, PhD, and DON A. ROCKWELL, MD

560 *Incest* SANDRA BAKER, MSW, LCSW

562 *In Memoriam*

564 *Volume Index*

Books Received, See Advertising Page 40

Information for Authors, See Advertising Page 26

★ CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA HAWAII AND NEVADA; ALASKA, MONTANA AND IDAHO; NEW MEXICO; OREGON; WASHINGTON; UTAH
(See Advertising Page 19)

★★ Official Journal of the California Medical Association, the Idaho Medical Association the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association and the Washington State Medical Association

We're not asking you for money.

Just a few words. To people who need us but don't know we exist.

We're Recording for the Blind. We're already helping more than 13,000 handicapped students. But there are a lot more out there who need our help.

You know who they are. In your work you come across students who are blind, dyslexic or physically unable to handle books. These are the students we help. Since they cannot read their textbooks, we do it for them. On tape. And we send the tapes to the students free of charge.

All we want you to do is tell eligible students about us. Have them contact: Student Services, RFB, Inc., 215 East 58th Street, N.Y., N.Y. 10022, (212) 751-0860. We'll take it from there.

It's such a little thing to ask.

Recording for the Blind is a non-profit organization. All contributions are tax-deductible.

Recording for the Blind, Inc.

an educational lifeline.

DRAMATIC NEW CLINICAL PROOF*

In the treatment of impetigo–

- **100% cure rate with Tegopen®** (cloxacillin sodium)
- **only a 60% cure rate with penicillin V-K**

As seen on admission

After one week of penicillin V-K therapy

Two weeks after initiation of TEGOPEN therapy

Treatment failure was judged to have occurred when lesions increased in size and/or number during the initial week of treatment with penicillin V-K. *No* treatment failures occurred with Tegopen.

*Data on file, Bristol Laboratories.

Brief Summary of Prescribing Information

TEGOPEN®
(cloxacillin sodium)
Capsules and Orat Sotution

For complete information, consult Official Package Circular (12) 9/11/75

INDICATIONS:

Although the principal indication for cloxacillin sodium is in the treatment of infections due to penicillinase-producing staphylococci, it may be used to initiate therapy in such patients in whom a staphylococcal infection is suspected (See Important Note below.)

Bacteriologic studies to determine the causative organisms and their sensitivity to cloxacillin sodium should be performed

IMPORTANT NOTE

When it is judged necessary that treatment be initiated before definitive culture and sensitivity results are known, the choice of cloxacillin sodium should take into consideration the fact that it has been shown to be effective only in the treatment of infections caused by pneumococci, Group A beta-hemolytic streptococci, and penicillin G-resistant and penicillin G-sensitive staphylococci If the bacteriology report later indicates the infection is due to an organism other than a penicillin G-resistant staphylococcus sensitive to cloxacillin sodium, the physician is advised to continue therapy with a drug other than cloxacillin sodium or any other penicillinase-resistant semi-synthetic penicillin.

Recent studies have reported that the percentage of staphylococcal isolates resistant to penicillin G outside the hospital is increasing, approximating the high percentage of resistant staphylococcal isolates found in the hospital. For this reason, it is recommended that a penicillinase-resistant penicillin be used as initial therapy for any suspected staphylococcal infection until culture and sensitivity results are known.

Cloxacillin sodium is a compound that acts through a mechanism similar to that of methicillin against penicillin G-resistant staphylococci. Strains of staphylococci resistant to methicillin have existed in nature and it is known that the number of these strains reported has been increasing. Such strains of staphylococci have been capable of producing serious disease, in some instances resulting in fatality. Because of this, there is concern that widespread use of the penicillinase-resistant penicillins may result in the appearance of an increasing number of staphylococcal strains which are resistant to these penicillins.

Methicillin-resistant strains are almost always resistant to all other penicillinase-resistant penicillins (cross-resistance with cephalosporin derivatives also occurs frequently). Resistance to any penicillinase-resistant penicillin should be interpreted as evidence of clinical resistance to all, in spite of the fact that minor variations in *in vitro* sensitivity may be encountered when more than one penicillinase-resistant penicillin is tested against the same strain of staphylococcus.

CONTRAINDICATIONS:

A history of a previous hypersensitivity reaction to any of the penicillins is a contraindication.

RESULTS OF ORAL THERAPY revealed a high percentage of treatment failures with penicillin V potassium, but *no* failures with Tegopen.

		Given Tegopen® *(cloxacillin sodium)*	Given *penicillin V-K*
Staphylococcus aureus	(78 patients)	39	39
Returned to clinic at one week		29†	38†
Treatment failure at one week		0	18 (47.4%)
Staphylococcus aureus* and *Streptococcus pyogenes	(9 patients)	4	5
Returned to clinic at one week		4	5
Treatment failure at one week		0	2 (40%)
No initial bacterial growth	(14 patients)	9	5
All 14 healed, regardless of which antibiotic was administered.			
Beta-hemolytic *Streptococcus*	(1 patient)	0	1
TOTALS:	**102 patients**	**52 patients**	**50 patients**

†Eleven patients did not return for their one-week checkup. These were all called by telephone, and their families reported the lesions had healed. One patient was dropped from the study, early, because of adverse reaction to medication.

STUDY: DESCRIPTION/PROTOCOL

- 102 nonselected subjects, with initial bacteriology as follows: 77% *Staphylococcus aureus*, 9% mixed *Staphylococcus aureus* and *Streptococcus pyogenes*, and 1% beta-hemolytic *Streptococcus*.‡
- All patients were given randomized therapy—Tegopen capsules or oral solution, or penicillin V-K tablets or oral solution, in recommended dosages according to body weight.
- All patients were evaluated after one week's therapy. If there was no improvement, therapy was switched to the other antibiotic. The "other antibiotic" proved to be Tegopen 100% of the time because no treatment failures had occurred with Tegopen.
- A final assessment of progress was made two weeks after initiation of Tegopen therapy.

‡The remainder, to equal 100%, consisted of 14 patients (13%) who exhibited no initial bacterial growth. These 14 were all healed, whether given Tegopen or penicillin V-K.

TEGOPEN®
(cloxacillin sodium)
–effective therapy for staph infections of the skin and skin structures

WARNING:
Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents, e.g., pressor amines, antihistamines, and corticosteroids.

Safety for use in pregnancy has not been established

PRECAUTIONS:
The possibility of the occurrence of superinfections with mycotic organisms or other pathogens should be kept in mind when using this compound, as with other antibiotics. If superinfection occurs during therapy, appropriate measures should be taken.

As with any potent drug, periodic assessment of organ system function, including renal, hepatic, and hematopoietic, should be made during long-term therapy

ADVERSE REACTIONS:
Gastrointestinal disturbances, such as nausea, epigastric discomfort, flatulence, and loose stools, have been noted by some patients. Mildly elevated SGOT levels (less than 100 units) have been reported in a few patients for whom pretherapeutic determinations were not made. Skin rashes and allergic symptoms, including wheezing and sneezing, have occasionally been encountered. Eosinophilia, with or without overt allergic manifestations, has been noted in some patients during therapy.

USUAL DOSAGE:
Adults: 250 mg. q.6h.

Children: 50 mg./Kg./day in equally divided doses q.6h. Children weighing more than 20 Kg. should be given the adult dose. Administer on empty stomach for maximum absorption.

N.B. INFECTIONS CAUSED BY GROUP A BETA-HEMOLYTIC STREPTOCOCCI SHOULD BE TREATED FOR AT LEAST 10 DAYS TO HELP PREVENT THE OCCURRENCE OF ACUTE RHEUMATIC FEVER OR ACUTE GLOMERULONEPHRITIS

SUPPLIED:
Capsules—250 mg. in bottles of 100. 500 mg. in bottles of 100.
Oral Solution—125 mg./5 ml. in 100 ml. and 200 ml. bottles.

BRISTOL®
Bristol Laboratories
Division of Bristol-Myers Company
Syracuse, New York 13201

Copyright © 1981, Bristol Laboratories

Bactrim™ succeeds

in recurrent urinary tract infections

from site to source

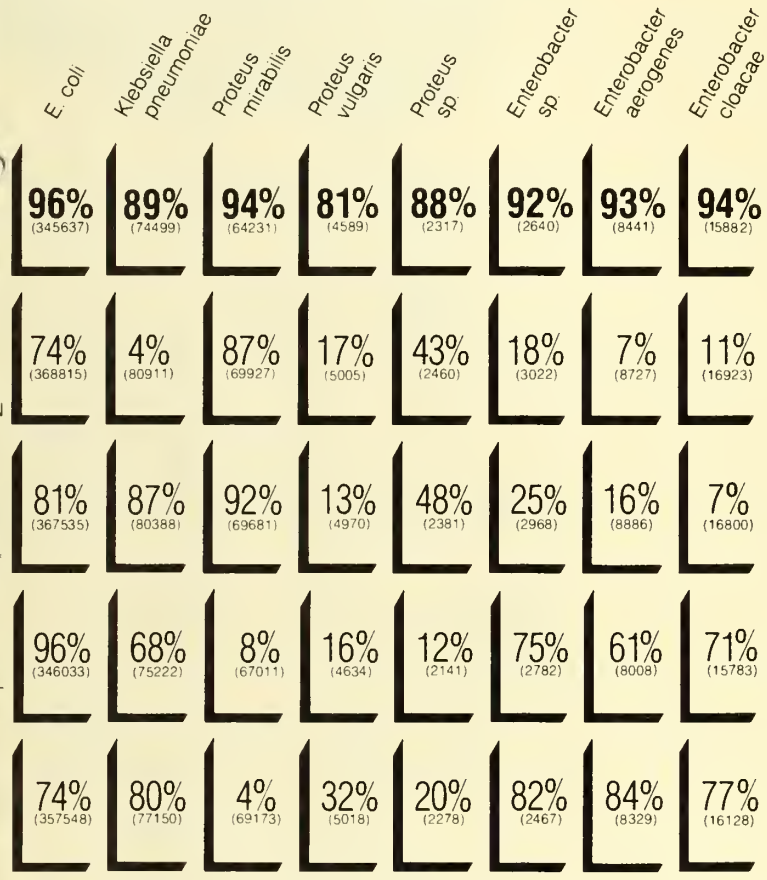
Bactrim reaches effective levels in urine, serum and renal tissue,[1] to combat infection throughout the urinary tract. The trimethoprim component enters vaginal secretions in therapeutic concentrations,[1] to prevent colonization of bacteria in the periurethral area, probably the major etiologic factor in recurrent UTI.[2,3] And in the fecal flora, Bactrim eradicates Enterobacteriaceae with no resulting emergence of resistant organisms and without adverse effect on the normal intestinal flora.

*due to susceptible *E. coli*, *Klebsiella-Enterobacter*, *Proteus mirabilis*, *P. vulgaris* and *P. morg*

a from 231 hospitals, compiled by an independent bacteriologic monitoring service, show:

ore isolates of more common uropathogens nsitive to Bactrim than to any other equently prescribed antimicrobial

nt of isolates of common uropathogens sensitive to Bactrim and to other antimicrobials



Numbers in parentheses indicate projected number of isolates tested with antibacterial.
Source: BacData Medical Information Systems, Inc., Summer 1980.
*Tested with cephalothin disc, recommended as representative of all cephalosporins.

Bactrim consistently proves its *in vitro* effectiveness against the organisms estimated to cause 90-95% of urinary tract infections: *E. coli*, *Proteus mirabilis*, *Klebsiella* and *Enterobacter* species.[4,5] Susceptibility tests are believed to correlate more closely with clinical results in urinary tract infections than in any other kind.[4]

No significant change seen in resistance patterns

Uropathogens sensitive to Bactrim have demonstrated no significant increased resistance *in vitro* after many years of use in patients with urinary tract infection.[6] In one study,[7] SMX/TMP (Bactrim), given over a period of four weeks, was not followed by emergence of resistant strains of Enterobacteriaceae—a result noted to correlate with clinical findings that in patients given SMX/TMP, urinary tract reinfections with resistant organisms are rare.

It is important to maintain adequate fluid intake during therapy. Bactrim is contraindicated during pregnancy at term, the nursing period, in patients hypersensitive to its components, and in infants under 2 months of age.

References: **1.** Rubin RH, Swartz MN: *N Engl J Med 303* 426-432, Aug 21, 1980. **2.** Dhalla S, Flynn JT. *NY State J Med 80*: 1087-1094, June 1980. **3.** Stamey TA. *J Urol 109*. 467-472, Mar 1973. **4.** Kunin CM. *Detection, Prevention and Management of Urinary Tract Infections*, ed 3. Philadelphia, Lea & Febiger, 1979, pp. 91, 140. **5.** Mayer TR. *Geriatrics* 35. 67-77, Mar 1980. **6.** BacData Medical Information Systems, Inc., Winter 1976-1977 to Summer 1980. **7.** Knothe H. *Infection 7* (Suppl 4): S321-S323, 1979.

Bactrim™ DS

160 mg trimethoprim and 800 mg sulfamethoxazole

maximizes results with B.I.D. convenience

ROCHE®

Please see summary of product information on following page.

Bactrim™ DS

160 mg trimethoprim and 800 mg sulfamethoxazole

Before preacribing, plesse conault complete product information, a summsry of which follows:

Indications and Usage: For the treatment of urinary tract infectiona due to susceptible strains of the following organisms: *Escherichia coli, Klebsiella-Enterobacter, Proteus mirabilis, Proteus vulgaris, Proteus morgsnii.* It ia recommended that initisl episodes of uncomplicated urinary trsct infections be treated with a single effective antibacterisl sgent rather than the combination. *Note:* The increasing frequency of resistant organisms limits the usefulness of all antibacterials, especially in these urinary tract infections

For acute otitis media in children due to susceptible atrains of *Haemophilus influenzse* or *Streptococcus pneumonise* when in phyaician's judgment it offers sn sdvantsge over other sntimicrobisls. Limited clinical informstion preaently availsble on effectiveneas of trestment of otitis media with Bactrim when infection la due to smpicillin-resistsnt *Haemophilus influenzae*. To date, there sre limited data on the safety of repested use of Bactrim in children under two yesrs of sge. Bactrim is not indicsted for prophyisctic or prolonged administrstion in otitis medis at any age.

For acute exacerbstions of chronic bronchitis in adults due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in physician's judgment it offers sn sdvantage over s single antimicrobial agent.

For enteritis due to ausceptible strains of *Shigella flexneri* and *Shigella sonnei* when sntibscterisl therapy is indicated.

Also for the treatment of documented *Pneumocystis csrinii* pneumonitia. To date, this drug has been teated only in pstients 9 months to 16 yesrs of sge who were immunoauppresaed by cancer therspy.

Contraindicstiona: Hypersensitivity to trimethoprim or sulfonamides; patients with documented megaloblastic anemia due to folate deficiency, pregnancy at term, nursing mothers because sulfonamides are excreted in human milk and may cause kernicterus; infants less than 2 months of age

Warnings: BACTRIM SHOULD NOT BE USED TO TREAT STREPTOCOCCAL PHARYNGITIS. Clinical studies show that patients with group A β-hemolytic streptococcal tonsillopharyngitis have higher incidence of bacteriologic failure when treated with Bactrim than do those treated with penicillin. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides. Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended; therapy should be discontinued if a significantly reduced count of any formed blood element is noted

Precsutions: *General:* Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In patients with glucose-6-phosphate dehydrogenase deficiency, hemolysis, frequently dose-related, may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function. Bactrim may prolong prothrombin time in those receiving warfarin; reassess coagulation time when administering Bactrim to these patients. *Pregnancy:* Teratogenic Effects: Pregnancy Category C. Because trimethoprim and sulfamethoxazole may interfere with folic acid metabolism, use during pregnancy only if potential benefits justify the potential risk to the fetus

Advsrss Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. *Blood dyscrasias.* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic reactions.* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gestrointestinel reactions:* Glossitis, stomatitis, nausea, emesis, ebdominal pains, hepatitis, diarrhea and pancreatitis. *CNS reections:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hellucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscelleneous reections:* Drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon. Due to certain chemical similarities to some goitrogens, diuretics (ecetazolemide, thiazides) and oral hypoglycemic egents, sulfonamides have ceused rare instances of goiter production, diuresis and hypoglycemia in patients; cross-sensitivity with these agents may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies

Dossge: Not rscommended for infants less than two months of age.

URINARY TRACT INFECTIONS AND SHIGELLOSIS IN ADULTS AND CHILDREN, AND ACUTE OTITIS MEDIA IN CHILDREN.

Adults. Usual adult dosage for urinary tract infections—1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 10-14 days. Use identical daily dosage for 5 days for shigellosis.

Children: Recommended dosage for children with urinary tract infections or ecute otitis media—8 mg/kg trimethoprim and 40 mg/kg sulfamethoxezole per 24 hours, in two divided doses for 10 days. Use identical daily dosage for 5 days for shigellosis.

For petients with renel impairment: Use recommended dosage regimen when creatinine clearance is above 30 ml/min. If creatinine clearance is between 15 and 30 ml/min, use one-half the usual regimen. Bactrim is not recommended if creatinine clearance is below 15 ml/min.

ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS IN ADULTS:

Usuel adult dosage: 1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 14 days

PNEUMOCYSTIS CARINII PNEUMONITIS:

Recommended dosage: 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours in equal doses every 6 hours for 14 days. See complete product information for suggested children's dosage table.

Supplisd: *Double Strength (DS) tablets*, each containing 160 mg trimethoprim and 800 mg sulfamethoxazole, bottles of 100; Tel-E-Dose® packages of 100; Prescription Paks of 20 and 28. *Tablets*, each containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 40. *Pediatric Suspension*, containing 40 mg trimethoprim and 200 mg sulfamethoxazole per teaspoonful (5 ml); cherry flavored—bottles of 100 ml and 16 oz (1 pint). *Suspension*, containing 40 mg trimethoprim and 200 mg sulfamethoxazole per teaspoonful (5 ml); fruit-licorice flavored—bottles of 16 oz (1 pint).

ROCHE

ROCHE LABORATORIES
Division of Hoffmann-La Roche Inc
Nutley, New Jersey 07110

Two convenient dosage forms: 100 mg (white) and 300 mg (peach) Scored Tablets

Tablets imprinted with brand name to assist in tablet identification.

Wellcome

Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

Mark your calendar . . .

The Eighth Annual University of Pittsburgh Symposium

EAR, NOSE, AND THROAT DISEASES IN CHILDREN

A 1981 Update

December 9-13, 1981

Rancho Las Palmas Resort
Rancho Mirage, Palm Springs, California

OTOLARYNGOLOGISTS AND PEDIATRICIANS

Update your knowledge of ear, nose, and throat diseases in children through scientific sessions, small-group workshops and demonstrations, and informal discussions.

UNIVERSITY OF PITTSBURGH FACULTY

C. D. Bluetone — J. L. Paradise — S. E. Stool
H. Felder — E. N. Myers

INVITED FACULTY

G. A. Gates (San Antonio) — J. O. Klein (Boston)

Accredited for 19 hours of ACCME Category 1 credit

For further information, contact: **DIVISION OF CONTINUING EDUCATION,** 1022 E Scaife Hall, University of Pittsburgh School of Medicine, Pittsburgh, PA 15261; telephone: (412) 624-2653.

CONTINUING MEDICAL EDUCATION

California, Hawaii, Nevada; Alaska, Montana, Idaho; New Mexico; Oregon; Washington; Utah

CALIFORNIA, HAWAII and NEVADA

This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000, ext. 146. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

August 4-11—**A Clinical Update on Anesthesia Practice.** California Society of Anesthesiologists Alaskan Cruise aboard the Island Princess. One week. 21 hrs. $250, CSA members; $350, nonmembers. Contact: Richard Manley, CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

August 23-26—**Clinical Neuroanesthesia.** California Society of Anesthesiologists at UCSD. Sunday-Wednesday. 24 hrs. $325, CSA members; $375, nonmembers. Contact: Richard Manley, CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

August 29-30—**Hemodynamic Monitoring—Pulmonary Artery Catheterization.** See "Of Interest to All," August 29-30.

September 12-13—**Weekend Seminar.** Calif. Society of Anesthesiologists at Sahara Hotel, Lake Tahoe. Saturday-Sunday. Contact: CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

CANCER

October 26-28—**Fifth Annual Cancer Symposium.** Scripps Memorial Hospital at Vacation Village, San Diego. Monday-Wednesday. 22 hrs. $300. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (714) 453-6222.

October 31—**4th Annual Manuel Levin Memorial Cancer Symposium.** Fresno Community Hospital. Saturday. Contact: Joann Ellis, Fresno Community Hosp., P.O. Box 1232, Fresno 93715. (209) 442-6000, ext. 5696.

November 13-14—**Current Concepts on Cancer Management: Successful Treatment and Its Consequences.** Mt. Zion Hospital and Medical Center at Fairmont Hotel, San Francisco. Friday-Saturday. 11 hrs. $150, before Sept. 15; $200, thereafter. Contact: Office of Cont. Med. Ed., Mt. Zion Hosp. and Med. Ctr., P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2405.

EMERGENCY MEDICINE

June 15-19—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $425.

June 26-27—**Orthopedics in Emergency Medicine—An In-Depth Review.** UCLA at Miramar-Sheraton Hotel, Santa Monica. Friday-Saturday. 14 hrs. $180.

June 29-July 3—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

July 24-26—**Advanced Cardiac Life Support Workshops.** Emergency Medical Systems at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact. EMS, 2310 Mason St., San Francisco 94133. (415) 956-5900.

July 27-28—**Advanced Cardiac Life Support.** Emergency Care Education Center at Queen Mary, Long Beach. Monday-Tuesday. 12 hrs. $130. Contact: ECEC, P.O. Box 9639, Marina Del Rey 90291. (213) 822-1312.

August 3-7—**Postgraduate Institute for Emergency Room Physicians, Symposium II.** UCSD. Monday-Friday. 40 hrs. $425.

September 14-18—**Postgraduate Institute for Emergency Room Physicians, Symposium I.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $425.

September 28-29—**Advanced Cardiac Life Support.** Emergency Care Education Center at Queen Mary, Long Beach. Monday-Tuesday. 12 hrs. $130. Contact: ECEC, P.O. Box 9639, Marina Del Rey 90291. (213) 822-1312.

October 2-3—**Symposium on Medical Emergencies.** UCLA at Miramar-Sheraton Hotel, Santa Monica. Friday-Saturday. 14 hrs. $180.

October 19-23—**Postgraduate Institute for Emergency Room Physicians, Symposium III.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $425.

October 24-31—**Emergency Medicine.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

November 23-24—**Advanced Cardiac Life Support.** Emergency

(Continued on Page 23)

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center 2801 Atlantic Ave., Long Beach 90801. (213) 595-3837.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

When she can't manage, you can.

The sweats. The hot flushes. The distress and discomfort of atrophic vaginitis. The possibility of osteoporosis.* The menopause.

For many women, it's a time of confusion and frustration. Counseling can help her overcome these feelings. But counseling *can't* stop vasomotor and vaginal symptoms, or retard bone loss*...the true signs of estrogen deficiency. And that's where she needs you most.

You're an expert at estrogen replacement. You know why it should be used. When it's best avoided. How to cycle therapy. Determine dosage. Check for contraindications and possible complications. Follow-up. You know when therapy should begin, and when it deserves to end.

Most of all, you know your patient—and when she needs the effective relief you can give her with PREMARIN.

When it comes to managing the estrogen-deficiency symptoms of the menopause, you've got what it takes.

*Conjugated Estrogens Tablets have been evaluated as probably effective for postmenopausal osteoporosis

Prescribed with care by physicians who care.

PREMARIN®
BRAND OF
CONJUGATED ESTROGENS TABLETS, U.S.P.
0.3 mg/0.625 mg/1.25 mg/2.5 mg

Please see following page for brief summary of prescribing information.

BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION, SEE PACKAGE CIRCULAR)

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA

Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year[1-3] This risk was independent of the other known risk factors for endometrial cancer These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade[4] The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4 5 to 13 9 times greater than in nonusers. The risk appears to depend on both duration of treatment[1] and on estrogen dose[3] In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration,[3] it therefore appears prudent to utilize such a regimen Close clinical surveillance of all women taking estrogens is important In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY

The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare[5,6] This risk has been estimated as not greater than 4 per 1000 exposures[7] Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis,[8-12] epithelial changes of the vagina and cervix Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects[13-16] One case control study[15] estimated a 4 7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion) Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000 In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

DESCRIPTION: PREMARIN (Conjugated Estrogens Tablets, U.S.P.) for oral administration contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications for use as follows.

Effective:

1. Moderate to severe *vasomotor* symptoms associated with the menopause (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions.)
2. Atrophic vaginitis
3. Kraurosis vulvae.
4. Female hypogonadism
5. Female castration
6. Primary ovarian failure
7. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease
8. Prostatic carcinoma—palliative therapy of advanced disease
9. Postpartum breast engorgement—Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy. Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens[19]

PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING)

"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions 1 Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease 2 Known or suspected estrogen-dependent neoplasia 3 Known or suspected pregnancy (See Boxed Warning). 4 Undiagnosed abnormal genital bleeding 5 Active thrombophlebitis or thromboembolic disorders 6 A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy)

WARNINGS: At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast,[17] although a recent study has raised this possibility[18] There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens[17]

Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement, it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement.[19-22] Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction[23-30] Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users[31,32] An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives.[33,34] If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization. Estrogens should not be used in persons with active thrombophlebitis, thromboembolic disorders, or in persons with a history of such disorders in association with estrogen use They should be used with caution in patients with cerebral vascular or coronary artery disease. Large doses (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown[35] to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis When doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a clear risk

Benign hepatic adenomas should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives[36] Increased blood pressure may occur with use of estrogens in the menopause[37] and blood pressure should be monitored with estrogen use A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases

PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed Conditions influenced by fluid retention such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc. Oral contraceptives appear to be associated with an increased incidence of mental depression[23a] Patients with a history of depression should be carefully observed Preexisting uterine leiomyomata may increase in size during estrogen use The pathologist should be advised of estrogen therapy when relevant specimens are submitted If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated Estrogens should be used with care in patients with impaired liver function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete.

The following changes may be expected with larger doses of estrogen:

a Increased sulfobromophthalein retention

b Increased prothrombin and factors VII, VIII, IX, and X, decreased antithrombin 3, increased norepinephrine-induced platelet aggregability

c Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered

d Impaired glucose tolerance

e Decreased pregnanediol excretion

f. Reduced response to metyrapone test

g Reduced serum folate concentration

h Increased serum triglyceride and phospholipid concentration.

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives: breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhea, premenstrual-like syndrome, amenorrhea during and after treatment, increase in size of uterine fibromyomata, vaginal candidiasis, change in cervical erosion and in degree of cervical secretion; cystitis-like syndrome; tenderness, enlargement, secretion (of breasts); nausea, vomiting, abdominal cramps, bloating; cholestatic jaundice, chloasma or melasma which may persist when drug is discontinued, erythema multiforme, erythema nodosum, hemorrhagic eruption, loss of scalp hair, hirsutism; steepening of corneal curvature, intolerance to contact lenses, headache, migraine, dizziness, mental depression, chorea, increase or decrease in weight, reduced carbohydrate tolerance, aggravation of porphyria, edema; changes in libido

ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females

DOSAGE AND ADMINISTRATION: 1 *Given cyclically for short term use only* For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0.3 to 1 25 mg or more daily).

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible

Administration should be cyclic (e.g. three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals

2 *Given cyclically:* Female hypogonadism Female castration. Primary ovarian failure Osteoporosis.

Female hypogonadism—2 5 to 7 5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration. If bleeding does not occur by the end of this period, the same dosage schedule is repeated. The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium.

If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U.S.P.), 2.5 to 7.5 mg daily in divided doses, for 20 days. During the last five days of estrogen therapy, give an oral progestin If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding.

Female castration and primary ovarian failure—1 25 mg daily, cyclically Adjust upward or downward according to response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

Osteoporosis (to retard progression)—1 25 mg daily, cyclically

3. *Given for a few days:* Prevention of postpartum breast engorgement—3 75 mg every four hours for five doses, or 1 25 mg every four hours for five days

4. *Given chronically:* Inoperable progressing prostatic cancer—1 25 to 2.5 mg three times daily.

Inoperable progressing breast cancer in appropriately selected men and postmenopausal women—10 mg three times daily for a period of at least three months

Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding

HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U.S.P.) No. 865—Each *purple* tablet contains 2.5 mg in bottles of 100 and 1,000 No. 866—Each *yellow* tablet contains 1 25 mg in bottles of 100 and 1,000 Also in unit dose package of 100. No 867—Each *red* tablet contains 0.625 mg in bottles of 100 and 1,000 Also in unit dose package of 100. No 868—Each *green* tablet contains 0.3 mg in bottles of 100 and 1,000.

PHYSICIAN REFERENCES: 1 Ziel, H.K., *et al.*: N Engl. J Med. *293*:1167-1170, 1975 2 Smith, D.C., *et al.*: N Engl. J. Med. *293*:1164-1167, 1975. 3 Mack, T.M., *et al.*: N Engl. J Med *294*:1262-1267, 1976. 4. Weiss, N.S., *et al.*: N Engl. J. Med *294*:1259-1262, 1976. 5 Herbst, A.L., *et al.*: N Engl. J. Med *284*:878-881, 1971. 6. Greenwald, P., *et al.*: N Engl J. Med *285*:390-392, 1971. 7. Lanier, A., *et al.*: Mayo Clin. Proc *48*:793-799, 1973 8 Herbst, A., *et al.* Obstet Gynecol *40*:287-298, 1972 9 Herbst, A., *et al.*: Am J. Obstet Gynecol *118*:607-615, 1974 10. Herbst, A., *et. al.*: N. Engl. J. Med *292*:334-339, 1975 11. Stafl, A., *et al.*: Obstet Gynecol. *43*:118-128, 1974 12 Sherman, A.I., *et. al.*: Obstet. Gynecol. *44* 531-545, 1974 13. Gal, I., *et al.*: Nature *216*:83, 1967 14 Levy, E.P, *et al.*: Lancet *1*:611, 1973 15. Nora, J., *et al.* Lancet *1*:941-942, 1973 16. Janerich, D.T., *et al* N Engl J Med *291*:697-700, 1974 17. Boston Collaborative Drug Surveillance Program: N Engl. J Med *290*:15-19, 1974 18 Hoover, R., *et al.* N Engl J. Med *295*:401-405, 1976. 19 Daniel, D G, *et al.* Lancet *2*:287-289, 1967. 20. The Veterans Administration Cooperative Urological Research Group J. Urol. *98*:516-522, 1967 21. Ballar, J.C.: Lancet *2*:560, 1967 22 Blackard, C., *et al.*: Cancer *26*:249-256, 1970. 23 Royal College of General Practitioners. J R Coll Gen Pract *13*:267-279, 1967. 23a Royal College of General Practitioners. Oral Contraceptives and Health, New York, Pitman Corp., 1974. 24 Inman, W.H.W., *et al.*: Br Med J *2*:193-199, 1968 25 Vessey, M.P., *et al.*: Br Med J. *2*:651-657, 1969 26 Sartwell, P.E., *et al.*: Am. J Epidemiol *90*:365-380, 1969 27. Collaborative Group for the Study of Stroke in Young Women: N Engl J Med. *288*:871-878, 1973 28 Collaborative Group for the Study of Stroke in Young Women. J.A.M.A *231*:718-722, 1975 29. Mann, J.I., *et al.*: Br. Med. J. *2*:245-248, 1975. 30. Mann, J.I., *et al.*: Br. Med J *2*:241-245, 1975. 31 Inman, W.H.W., *et al.*: Br. Med. J *2*:203-209, 1970 32 Stolley, P.D., *et al.*: Am. J Epidemiol. *102*:197-208, 1975 33 Vessey, M.P, *et al* Br Med J 3:123-126, 1970. 34 Greene, G.R., *et al.*: Am J. Public Health *62*:680-685, 1972 35. Coronary Drug Project Research Group J.A.M.A *214*:1303-1313, 1970 36 Mays, E.T., *et al.*: J A M A *235*:730-732, 1976. 37 Pfeffer, R.I., *et al* Am J Epidemiol *103*:445-456, 1976

7457/181

Ayerst AYERST LABORATORIES
New York, N.Y. 10017

(Continued from Page 19)

Care Education Center at Queen Mary, Long Beach. Monday-Tuesday. 12 hrs. $130. Contact: ECEC, P.O. Box 9639, Marina Del Rey 90291. (213) 822-1312.

December 7-10—**Postgraduate Institute for Emergency Room Physicians, Symposium IV.** UCSD at Vacation Village, San Diego. Monday-Thursday.

December 14-18—**Postgraduate Institute for Emergency Room Physicians, Symposium II.** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $425.

MEDICINE

June 26-28—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Sheraton, Anaheim. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

July 10-11—**Frontiers in Cardiology.** San Diego Heart Institute, Alvarado Community Hospital, at Hyatt Islandia Hotel, San Diego. Friday-Saturday. Contact: Allan L. Simon, MD, San Diego Heart Institute, Alvarado Community Hosp., 6655 Alvarado Rd., San Diego 92120. (714) 287-3270.

July 11-18—**Endocrine Metabolic Course.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 25 hrs. $350.

July 13-17—**Third International Psoriasis Symposium.** STAN. Monday-Friday.

July 18-25—**Cardiovascular Medicine and Surgery: An Advanced Course.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 23 hrs. $295.

July 31-August 4—**Internal Medicine Update.** American College of Physicians at Kihei, Maui, Hawaii. Friday-Tuesday. Contact: ACP, 4200 Pine St., Philadelphia 19104.

August 7-8—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Doubletree Inn, Monterey. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

August 12-15—**Workshop in Medical Mycology/Dermatomycology.** Memorial Hospital Medical Center-UCI Center for Health Education at Newporter Inn, Newport Beach. Wednesday-Saturday. Contact: Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

August 15-21—**Neuropsychiatric Issues in the Law, Education and Medicine: Hyperactivity and Dyscontrol Syndrome.** See Psychiatry, August 15-21.

August 21-22—**Cardiac Rehabilitation.** International Medical Education Corp. at Sheraton, Anaheim. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

August 25-June 29—**Seminars in Nephrology.** USC at Holiday Inn, Los Angeles/Westwood. Tuesday evenings; five sessions. 12½ hrs. $70.

September 5-8—**Advances in Internal Medicine.** UCSD. Saturday-Tuesday.

September 5-9—**Dermatopathology.** UCD at Silverado Country Club, Napa. Saturday-Wednesday.

September 9—**New Concepts in the Diagnosis and Management of Peripheral Vascular Disease.** LLU. Wednesday. 4 hrs.

September 14-17—**Current Concepts, Controversies and Clinical Strategies in Gastroenterology.** Cedars-Sinai Medical Center at Beverly Hilton Hotel, Beverly Hills. Monday-Thursday. 27 hrs. $450. Contact: Lore Kahane, Cedars-Sinai Med. Ctr., Rm. 2049, P.O. 48750, Los Angeles 90048. (213) 855-5547.

September 18—**Diabetes and the Kidney—14th Annual Symposium on Renal Disease.** National Kidney Foundation of Northern Calif. at Hilton, San Francisco. Friday. $60. Contact: Nat'l Kidney Fndn. of No. Calif., 856 Stanton Rd., Burlingame 94010. (415) 697-0110.

September 18-20—**Cardiac Ischemia and Arrhythmias—Current Concepts for Diagnosis and Treatment.** International Medical Education Corp. at Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

September 25—**Hypertension.** UCD. Friday.

September 25-26—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Holiday Inn, San Francisco. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112, (800) 525-8646.

October 3—**4th Annual Heart Symposium.** Northridge Hospital at Century Plaza Hotel, Los Angeles. Saturday. Contact: Dept. of Med. Ed., Northridge Hospital, 18300 Roscoe Blvd., Northridge 91328. (213) 885-8500.

October 3-10—**Cardiology—1981.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 28 hrs. $350.

October 6-7—**48th Annual Fall Symposium and 13th George C. Griffith Scientific Lecture.** American Heart Assn., Greater Los Angeles Affiliate, at Hilton, Los Angeles. Tuesday-Wednesday. 11 hrs. $125, AHA member; $150, nonmember. Contact: Mary Frances Flynn, AHA, Greater LA Affiliate, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

October 9-11—**California Society of Internal Medicine—Annual Meeting.** Marriott's Rancho Las Palmas Resort, Rancho Mirage. Friday-Sunday. Contact: Carol Parlette, Exec. Dir., CSIM, 703 Market St., Suite 1412, San Francisco 94103.

October 12-16—**An Advanced Course for Internists.** STAN. Monday-Friday. 25 hrs.

October 14—**Thrombophlebitis and Thromboembolic Disease.** LLU. Wednesday. 4 hrs.

October 14-December 16—**Nephrology.** UCLA. Wednesday evenings.

October 16-17—**Advances in Internal Medicine.** So. Calif. Permanente Medical Group at Century Plaza Hotel, Los Angeles. Friday-Saturday. Contact: Shirley Gach, Education and Research, SCPMG, 4747 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

October 16-18—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Sahara Hotel, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

October 17-24—**Lymphoproliferative Disorders.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

October 18-22—**Pacific Dermatologic Association—Annual Meeting.** Reno. Monday-Thursday. Contact: Florence Beardsley, Exec. Sec., PDA, 180 Mark Twain Ave., Reno 89509. (702) 323-2461.

October 19-22—**Electrocardiography: Core Curriculum and Self-Assessment.** American College of Cardiology at Mark Hopkins Hotel, San Francisco. Monday-Thursday. Contact: Registration Sec., Extramural Programs Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014. (301) 897-5400.

October 25-29—**American College of Chest Physicians.** Hilton Hotel, San Francisco. Sunday-Thursday. 30 hrs. Contact: Dept. of Education, ACCP, 911 Busse Highway, Park Ridge, IL 60068. (312) 698-2200.

October 29-31—**Cardiology Update—1981.** American College of Cardiology and UCSF at Quail Lodge, Carmel Valley. Thursday-Saturday. Contact: Registration Sec., Extramural Programs Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014. (301) 897-5400.

November 6-8—**Cardiac Ischemia and Arrhythmias—Current Concepts for Diagnosis and Treatment.** International Medical Education Corp. at Sahara Hotel, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

(Continued on Page 41)

DIABETES and the KIDNEY

14th Annual Symposium
ON
RENAL DISEASE

SPONSORED BY THE

NATIONAL KIDNEY FOUNDATION
of Northern California

Friday, September 18
San Francisco Hilton Hotel
San Francisco, CA

Subjects and faculty are:

- **Diabetes—Prevalence, Genetics and Classification,**
  Dr. Clinton Young, San Francisco
- **Diabetic Vascular Diseases,**
  Dr. Marvin Siperstein, San Francisco
- **Diabetic Nephropathy, Morphology and Functional Correlates of Progression,**
  Dr. Bryan Myers, Stanford
- **Renal Retinal Syndrome,**
  Dr. Eli Friedman, New York
- **Treatment of Diabetic Retinopathy,**
  Dr. John Cavender, San Francisco
- **Is Diabetic Nephropathy Preventable?**
  Dr. Eli Friedman
- **Artificial Pancreas,**
  Dr. Clinton Young
- **Renal Transplant in the Diabetic,**
  Dr. John Najarian, Minneapolis
- **Pancreatic Transplant in the Diabetic,**
  Dr. Roy Calne, Cambridge, England.

Symposium Director:
DR. BARRY LEVIN, Presbyterian Hospital, San Francisco
Tuition: Physicians $60, Allied Health Professionals, $25

This course is acceptable for 9 hours Category I Credit towards the CMA. Continuing education credit pending for Allied Health Professionals.

For further Information and Registration contact:

National Kidney Foundation of Northern California
856 Stanton Road
Burlingame, CA 94010
(415) 697-0110

Workshop entitled

MARRIAGE & DIVORCE COUNSELLING

will be held in

SANTA FE, NEW MEXICO

August 7 through 9, 1981

This program has been reviewed and is acceptable for 13 elective hours by the AAFP.

Contact **DR. THOMAS M. PICK,**
474 MAIN ST.
GREENFIELD, MASS 01301
PHONE (413) 774-2889

Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown, but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

Ativan® (lorazepam) for Anxiety

Dosage: **Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.**

How Supplied: **0.5, 1.0 and 2.0mg tablets.**

Copyright © 1981, Wyeth Laboratories.
All rights reserved

Wyeth Laboratories
Philadelphia PA 19101

our practical reasons to prescribe Ativan® for (lorazepam) Ⓘⓥ Anxiety*

1 No interaction with more than 300 drugs†

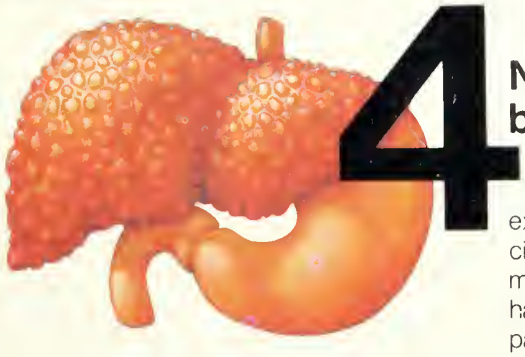
In clinical studies, Ativan was given concomitantly with hundreds of medications, including gastrointestinal and cardiovascular, with no reported interactions. Whereas the interaction of diazepam and cimetidine has been shown to cause increased sedation in patients taking both drugs, the clearance of Ativan is not delayed by Tagamet.‡

2 Lets most patients stay active

Long-acting benzodiazepines have long-acting metabolites with activity which can produce excessive accumulation that may lead to unwanted sedation. Ativan® has no active metabolites, reaches steady state in 2 to 3 days and usually does not cause oversedation. Also, the shorter half-life of Ativan is consistent with b.i.d. dosage, so drug hangover is seldom a problem the next morning.

3 Not appreciably affected by aging

Unlike the long-acting benzodiazepines—diazepam Ⓘⓥ, chlordiazepoxide Ⓘⓥ, clorazepate Ⓘⓥ and prazepam Ⓘⓥ—the metabolism and clearance of Ativan are not appreciably affected by the aging process.



4 Not significantly affected by liver dysfunction

Ativan® is metabolized in one simple step to an inactive glucuronide; its absorption and excretion are not significantly altered by cirrhosis or hepatitis. By contrast, the metabolism of diazepam and chlordiazepoxide has been reported to be significantly altered in patients with liver dysfunction.

See important information on following page.

Wyeth Laboratories
Philadelphia, PA 19101

TM

nxiety or tension associated with the stress of everyday life usually does not require
eatment with an anxiolytic.
benzodiazepines, however, produce additive effects when given with CNS depressants,
ch s barbiturates or alcohol.

ar (cimetidine) is a registered trademark of Smith Kline & French Laboratories,
ist of SmithKline Corporation.

pyright © 1981, Wyeth Laboratories. All rights reserved

THE WESTERN JOURNAL OF MEDICINE
INFORMATION FOR AUTHORS

Submitting Manuscripts

Manuscripts for consideration should be sent to the editor, Malcolm S. M. Watts, MD, 731 Market Street, San Francisco, California 94103. The transmittal letter should designate one person as correspondent and include complete address, with ZIP code and telephone number.

In view of *The Copyright Revision Act of 1976,* transmittal letters should contain the following language: "In consideration for reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns or otherwise conveys all copyright ownership to THE WESTERN JOURNAL OF MEDICINE in the event that such work is published by the journal." This statement should be signed by *all* the authors.

Authors are urged to seek clarity and succinctness in all manuscripts regardless of subject matter or format, and to give close attention to syntax, grammar and spelling.

Preparing Manuscripts

The original manuscript and *two* copies should be submitted on heavy bond paper (8½ by 11 inches, *not* erasable), typed double-spaced throughout (including legends, tables and references) on one side of the paper, with 1½-inch margins. Ordinarily, articles should not exceed 3,000 words (less than 15 text pages, typed double-spaced). Under exceptional circumstances only will articles longer than 4,000 words be published. Pages should be numbered consecutively, beginning with the title page.

Style

Abbreviations. Use of abbreviations should be minimized. If they are necessary, abbreviations should be spelled out at first mention, with the abbreviation itself immediately following in parentheses.

Weights and measures. All measurements should be given in metric units. English equivalents should be given parenthetically if the measurements were originally done in English units.

Temperatures. Temperature readings should be given first in Celsius, followed by the Fahrenheit equivalent in parentheses.

Drug names. If the trade name of a drug is used, the generic name should be given first, followed by the trade name in parentheses. Trade names are capitalized, generic names are not.

Title Page

Titles are best when brief and concise. The title page should include the full name of the author(s), with degrees, academic or professional titles, complete addresses and any institutional or other affiliations. The complete name and address of the person who will handle reprint requests also should appear on this page.

Abstract

The abstract (approximately 150 words) should be a short summary, saying in brief what is said at length in the body of the article—rather than such and such "is discussed," "is presented" or "was investigated."

Tables and Figures

Tables

Each table should be typed on a separate sheet of paper, be numbered consecutively in Arabic numerals, have a brief descriptive title and have its position indicated in the text.

Illustrations (Figures)

Three sets of clear, unmounted black and white glossy prints of figures should be submitted (preferably 5 by 7 inches, but no larger than 8½ by 11 inches). For line drawings, original artwork or glossy prints are acceptable. Illustrations should be numbered consecutively in Arabic numerals and their position indicated in the text. Figure number, first author's name and top of the photo should be shown on the reverse side of each illustration. Recognizable photographs of patients are to be masked and written permission for publication obtained from the patients.

Legends

All legends for figures should be typed together on a separate sheet of paper. Magnification and stain for photomicrographs should be indicated in parentheses.

Permission for Reproduction

If an illustration or table has been used previously in another publication, written permission for its use must be obtained from the publisher, and should accompany the manuscript. The source should be acknowledged in the legend if it can be done briefly by citation of a reference number. Otherwise, acknowledgment is made at the end of the figure legend or at the bottom of the table.

References

References should be limited to those cited in the text. They must be typed double-spaced and numbered consecutively as they appear in the manuscript. (See examples below for style.) Abbreviations of journal titles should conform to those used in *Index Medicus.*

Journal Articles

Note handling of multiple authorship. If more than three authors are listed as contributors, use "et al" to designate those names after the first three. Also note capitalization, punctuation, mention of inclusive page numbers, and month and year of publication. Separate the subtitle from the title by either a dash or a colon. Use colon *only* if it appears in the original citation.

1. Jones JS, Anderson HW, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 292:444-456, Apr 26, 1978

2. Graybill JR, Alford RH, Smith RG, et al: Cell-mediated immunity in cryptococcosis: A brief review. Cell Immunol 7: 76-79, Sep 1978

Books

Note handling of "edition," "editor(s)," and "volume," as well as appropriate sequence of reference information and capitalization of chapters and titles.

3. Berne EJ, Smith TL: Role playing in therapy, chap 2, Principles of Group Therapy. New York, Oxford University Press, 1966, pp 35-51 *(author of chapter same as author of book)*

4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, IL, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

Pamphlets, Monographs or Books With No Given Author

5. AMA Department of Drugs: AMA Drug Evaluation, 3rd Ed. Littleton, MA, Publishing Sciences Group, Inc, 1977 *(corporate author)*

6. Compilation of Standard Definitions, 3rd Ed. Philadelphia. American Society for Testing and Materials, 1976 *(no given author; give name and place of publisher)*

Articles in Press or Accepted for Publication

Any article accepted for publication should include the name of the journal (appropriately abbreviated) in which it will appear, and the phrase "in press" or "accepted for publication" in place of the date of publication.

Personal Communications and Unpublished Data

This information should *not* be included in the reference list but should be given in parentheses within the body of the text. Date of communication, whether it was personal or written, and the person's name, highest academic degree and professional affiliation should be provided.

Acknowledgments

It is the policy of the *WJM* not to print acknowledgments, the feeling being that if a person has contributed enough to a paper to be mentioned, he or she should be included among the authors, or the contribution should be mentioned in the body of the paper or in a footnote.

Correspondence

Brief manuscripts commenting on articles that have appeared in the journal, containing information of interest to physicians or discussing issues of the day will be considered for publication. Very short reports of cases, clinical experience, clinical studies, adverse effects and the like also will be considered. Items for the Correspondence section should not exceed 600 words and should have no more than five bibliographic references and one figure or table.

Author Responsibility

Authors are responsible for all statements made in articles. Manuscripts are considered for publication with the explicit understanding that they are original, have not been published previously and are not simultaneously under consideration by any other publication.

All accepted manuscripts are subject to copy editing, and authors are sent edited galleys for approval. No changes will be made after the final, edited version has been approved by the author.

Reprints

If reprints are desired, they must be paid for by the author. A reprint order form with schedule of prices is sent to the author when the article is published. Authors are responsible for handling requests for reprints of their articles.

HOW TO CURE BILLING PAINS.

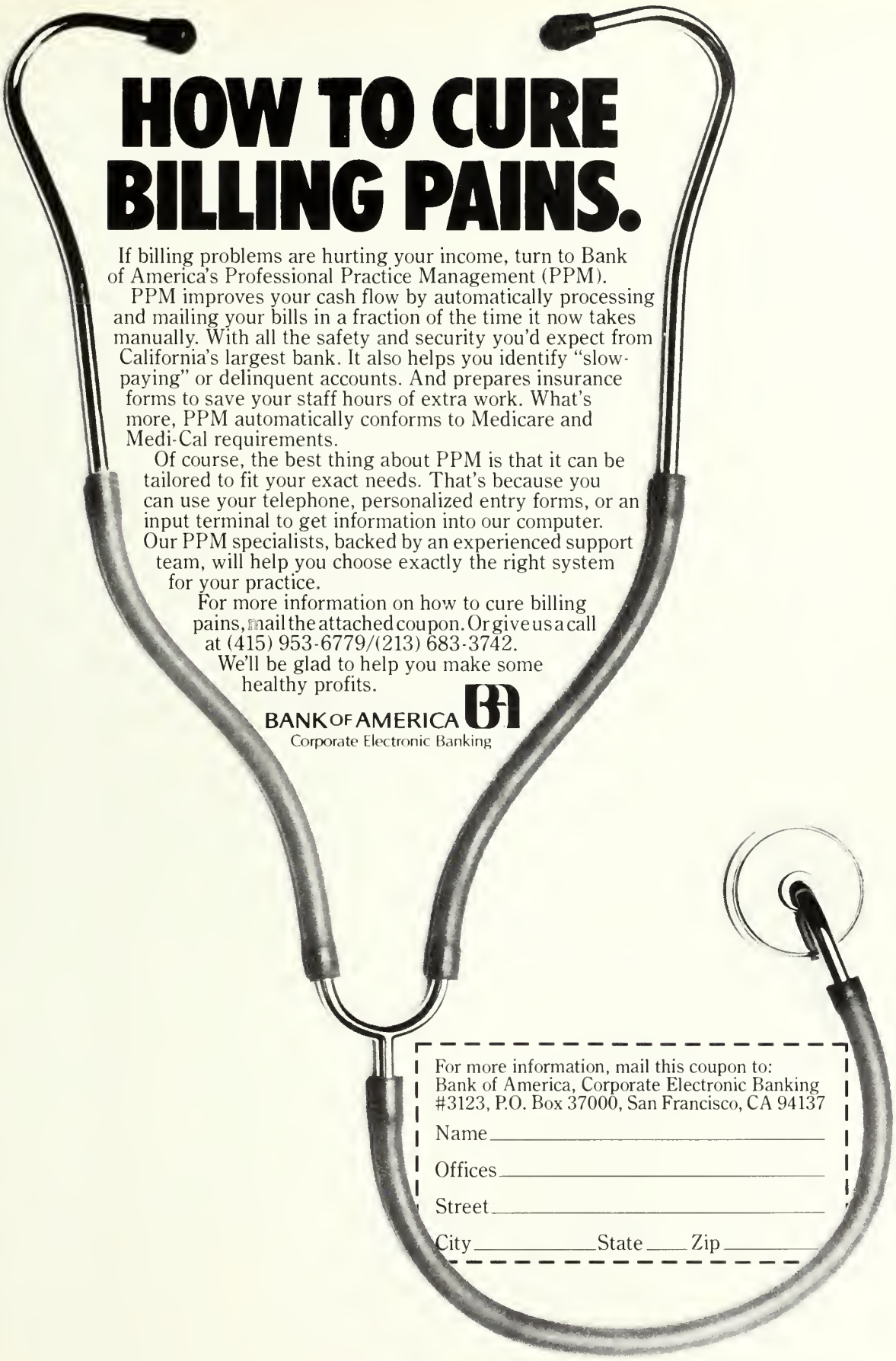
If billing problems are hurting your income, turn to Bank of America's Professional Practice Management (PPM).

PPM improves your cash flow by automatically processing and mailing your bills in a fraction of the time it now takes manually. With all the safety and security you'd expect from California's largest bank. It also helps you identify "slow-paying" or delinquent accounts. And prepares insurance forms to save your staff hours of extra work. What's more, PPM automatically conforms to Medicare and Medi-Cal requirements.

Of course, the best thing about PPM is that it can be tailored to fit your exact needs. That's because you can use your telephone, personalized entry forms, or an input terminal to get information into our computer. Our PPM specialists, backed by an experienced support team, will help you choose exactly the right system for your practice.

For more information on how to cure billing pains, mail the attached coupon. Or give us a call at (415) 953-6779/(213) 683-3742. We'll be glad to help you make some healthy profits.

BANK OF AMERICA
Corporate Electronic Banking



For more information, mail this coupon to:
Bank of America, Corporate Electronic Banking
#3123, P.O. Box 37000, San Francisco, CA 94137

Name_____

Offices_____

Street_____

City_____ State____ Zip_____

Bank of America NT&SA Member FDIC

Something
happens...

Depressive,
anxiety
AND
somatic
symptoms respond
rapidly...

without a phenothiazine

A special quality of relief typically comes early to anxious depressed patients treated with Limbitrol. For example, core depressive symptoms—feelings of guilt and worthlessness—often respond within a week. So do insomnia, anorexia, agitation, and psychic and somatic anxiety. And as the anxious depression responds, so, often do the related somatic symptoms—headache, backache, G.I. upset, palpitations.* No less important to the patient's progress is the enhanced compliance that comes with the early sense of well-being.

With Limbitrol, these striking results are obtained without the phenothiazines contained in other dual medications. The causal relationship between the phenothiazines and extrapyramidal side effects, including tardive dyskinesia, is well established. In contrast, the reported incidence of these adverse reactions with Limbitrol or either of its components is rare.

Patients should be cautioned about the combined effects with alcohol or other CNS depressants and about activities requiring complete mental alertness, such as operating machinery or driving a car.

*Data on file, Medical Department, Hoffmann-La Roche Inc.

Please see summary of product information on following page.

in moderate depression and anxiety

Limbitrol® IV

Tablets 5-12.5 each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)

Tablets 10-25 each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt)

A special quality of relief

ROCHE®

LIMBITROL® TABLETS Tranquilizer–Antidepressant
Before prescribing, please consult complete product information, a summary of which follows:
Indications: Relief of moderate to severe depression associated with moderate to severe anxiety.
Contraindications: Known hypersensitivity to benzodiazepines or tricyclic antidepressants. Do not use with monoamine oxidase (MAO) inhibitors or within 14 days following discontinuation of MAO inhibitors since hyperpyretic crises, severe convulsions and deaths have occurred with concomitant use, then initiate cautiously, gradually increasing dosage until optimal response is achieved. Contraindicated during acute recovery phase following myocardial infarction.
Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients. (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).
***Usage in Pregnancy:* Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**
Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage; withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline; symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).
Precautions: Use with caution in patients with a history of seizures; in hyperthyroid patients or those on thyroid medication; and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. Concomitant use with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12.
In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.
Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.
The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs:
Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.
Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido.
Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.
Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.
Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.
Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.
Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.
Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female and elevation and lowering of blood sugar levels.
Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.
Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.
Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single h.s. dose may suffice for some patients. Lower dosages are recommended for the elderly. Limbitrol 10-25, initial dosage of three to four tablets daily in divided doses, increased to six tablets or decreased to two tablets daily as required. Limbitrol 5-12.5, initial dosage of three to four tablets daily in divided doses, for patients who do not tolerate higher doses.
How Supplied: White, film-coated tablets, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt) and blue, film-coated tablets, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)—bottles of 100 and 500, Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10, Prescription Paks of 50.

ROCHE®
ROCHE PRODUCTS INC.
Manati, Puerto Rico 00701

EMC — PROVIDENCE
3rd Annual
Endocrine Symposium
on
Metabolic Bone Disease
October 1 & 2, 1981
San Francisco Hilton Hotel
San Francisco, California

Speakers Include:
Henry Bourne, M.D.
Arnold Brickman, M.D.
Jack W. Coburn, M.D.
Leonard J. Deftos, M.D.
Julie Glowacki, Ph.D.
Stavros Manolagas, M.D., Ph.D.
Frederick Singer, M.D.

Topics Include:
Calcium Regulating Hormones
Mechanisms of Bone Formation and Resorption
Second Messengers in Bone Metabolism
Paget's Disease
Osteoporosis
Osteomalacia
Parathyroid Bone Disease
Bone Disease in Renal Failure
Neoplastic Bone Diseases

Sponsored By:
Endocrine-Metabolic Center
and
Providence Hospital of Oakland

For Information and Registration Information Contact:
Endocrine-Metabolic Center
3100 Summit Street
Oakland, California 94623
(415) 835-4940

This Symposium has been approved for 16 hours of Category I credit

PRACTICE MADE PERFECT™

FBN Data System's Medical Billing Systems range in price from between $200 to $700 per month on a 5 year lease. These proven packages with our own "Lifeline" support are available for immediate demonstration and delivery. Call Sandy Schupper at 714 770-3110

FBN DATA SYSTEMS™

24601 Raymond Way, El Toro CA 92630
Telephone: 714 770-3110

SUBSCRIPTION ORDER BLANK

To Receive

THE WESTERN Journal of Medicine

or to Give it as a Gift,

Return this coupon.

Please mail this coupon with enclosed payment to

WJ6/81

THE WESTERN Journal of Medicine

731 Market Street, San Francisco, California 94103

Subscriptions (U.S. and Canada) $10 Foreign subscriptions $18

nclosed is $_____ to cover _____ subscriptions. Subscription renewal ☐

end subscription

O: _____

_____

treet

_____

ity State Zip

_____

ype of practice

ift Card to read "From _____"

egular subscription ☐ Foreign subscription ☐

TO: _____

_____

Street

_____

City State Zip

_____

Type of practice

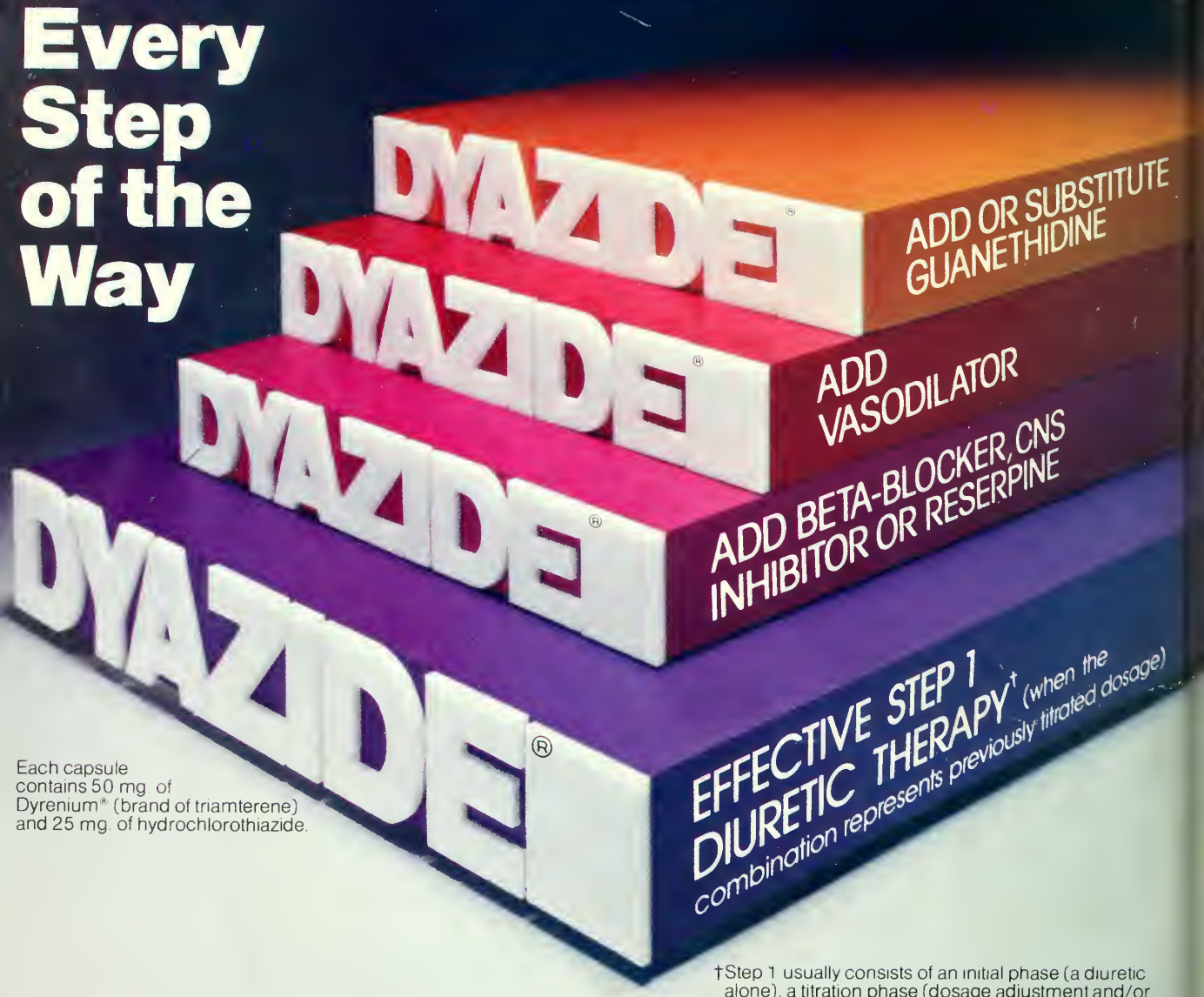
Gift Card to read "From _____"

Regular subscription ☐ Foreign subscription ☐

Please allow six weeks for subscriptions to begin

In Hypertension*...When You Need to Conserve K^+

Every Step of the Way



Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

†Step 1 usually consists of an initial phase (a diuretic alone), a titration phase (dosage adjustment and/or addition of a K^+ supplement or K^+-sparing agent), and a maintenance phase (a diuretic alone or in combination with a K^+ supplement or K^+-sparing agent).

Serum K^+ and BUN should be checked periodically (see Warnings).

Before prescribing, see complete prescribing information in SK&F Co. literature or *PDR*. The following is a brief summary.

* **WARNING**

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K^+ frequently, both can cause K^+ retention and elevated serum K^+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other, serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia, although uncommon, has been reported. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis and of impotence have been reported with the use of 'Dyazide' although a causal relationship has not been established.

Supplied: Bottles of 1000 capsules. Single Unit Packages (unit-dose) of 100 (intended for institutional use only). Patient-Pak™ unit-of-use bottles of 100.

© SK&F Co., 1980

SK&F CO.
a SmithKline company
Carolina, P.R. 00630

THE WESTERN
Journal of Medicine

Refer to: Tanner MH, Pierce BJ, Hale DC: Toxic shock syndrome. West J Med 134:477-484, Jun 1981

Toxic Shock Syndrome

MARTHA H. TANNER, MD; BARBARA J. PIERCE, RN, *and*
DeVON C HALE, MD, *Idaho Falls, Idaho*

Eight cases of toxic shock syndrome, confirmed by Center for Disease Control criteria, involved women who were menstruating and were tampon users. Each patient had severe febrile illness with rash, associated hypotension, renal and liver function abnormalities, pharyngitis and vaginitis. An examination of the literature indicates that cases that were reported as adult Kawasaki disease may actually have been toxic shock syndrome.

TOXIC SHOCK SYNDROME was originally described by Todd and co-workers[1] in children and was thought to be related to toxin-producing *Staphylococcus aureus* infections. Subsequently, the syndrome has been described in menstruating women[2,3] and has been associated with tampon use and positive vaginal cultures for *S aureus*.[4,5]

The cases of eight patients with acute illness associated with menses, shock, diffuse redness or scarlatiniform rash, and clinical and laboratory abnormalities involving most organ systems are presented. Because all the cases are similar, we will describe only one in detail and will summarize the others. We hope the case report will help physicians recognize this syndrome.

Report of a Case

A 40-year-old woman was seen in October 1979 because of fever and low blood pressure. The patient had had a sore throat and fever during two previous menstrual cycles, beginning in May 1979. She was treated with penicillin during one of these episodes. She became ill again in October, one day following the onset of her menstrual period. Dysuria, chills, fever, myalgia, vomiting and diarrhea developed. She was admitted to a local hospital two days after becoming ill. On admission, she was febrile, her skin was flushed and she was hypotensive, with orthostatic lightheadedness. She had pyuria and was treated for a urinary tract infection with co-trimoxazole and cefazolin. Over the next 12 hours her blood pressure remained 60/40 mm of mercury, her fever persisted and the diffuse redness increased.

The patient was referred to a regional hospital. On admission there, blood pressure was 80/40 mm of mercury, temperature was 38.9°C (102°F) and her respiratory rate was 22 per minute. The most striking aspects of her appearance were a generalized erythema and edema of the face. The patient was irritable, uncooperative and in considerable discomfort from diffuse pain. However, she was mentally alert and her recent memory appeared intact. Also noted were a diffuse redness of the throat without edema, supple neck, clear chest, bilateral costovertebral angle tenderness and unremarkable heart sounds. There was bilateral lower quadrant tenderness of the abdomen with questionable rebound in the left lower quadrant, but there was no distention. No circumoral pallor was noted, nor were the conjunctiva noted to be injected. A foul-smelling tampon was removed. Findings of a pelvic examination included a mucopurulent vaginal discharge and a uterus that was very tender on manipulation.

Laboratory findings on admission are sum-

From the Department of Infectious Disease, Riverview Hospital, Idaho Falls, Idaho.

Submitted, revised, December 8, 1980.

Reprint requests to: Martha Tanner, MD, 900 Memorial Drive, Idaho Falls, ID 83401.

ABBREVIATIONS USED IN TEXT

ASO = antistreptolysin
CDC = Center for Disease Control

marized in Table I (patient 4). The hemoglobin value was normal. Analysis of urine showed a pH of 5, 5 to 8 leukocytes per high-power field, and proteinuria (1+). Electrolyte values included sodium 124, potassium 3.9, chloride 92 and carbon dioxide content 18 mEq per liter. Antistreptolysin (ASO) titer was negative. Vaginal cultures were positive for *Staphylococcus aureus* and *Klebsiella pneumoniae*. Blood, urine and pharynx cultures were negative. An x-ray study of the chest and intravenous pyelogram (IVP) done on admission showed no abnormalities. The electrocardiogram indicated sinus tachycardia and nonspecific ST-T changes.

During her first 24 hours in the regional hospital she was treated with ampicillin and gentamicin and was given supportive care. The patient's irritability and uncooperativeness improved, and she became afebrile. On the day after admission the following occurred: a spontaneous diuresis of 4 liters with the patient's weight dropping from 57 to 54 kg, resolution of the generalized edema, the appearance of a macular rash and the development of mild dyspnea associated with perihilar infiltrates on x-ray studies of the chest. By discharge, these signs had resolved and renal function had returned to normal. Abdominal tenderness persisted two days into the hospital stay. The patient reported peeling of the skin of her hands following discharge from the hospital.

TABLE 1.—*Laboratory Findings for Eight Patients With Toxic Shock Syndrome*

Finding	Patient (1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Serum creatinine/BUN (mg/dl)	3.2/33	ND/23	ND/55	4.1/57.9	3.1/71.0	2.2/ND	1.4/4	1.5/22
Bilirubin direct/indirect (mg/dl)	ND/0.5	WNL	WNL	1.0/0.3	3.3/0.9	1.3/2.2	WNL	1.0/1.7
Alkaline phosphatase (normal) (IU/liter)	WNL	WNL	WNL	546 (258)	544 (100)	WNL	141 (100)	WNL
SGPT (normal) (IU/liter)	WNL	WNL	100 (40)	WNL	100 (32)	130 (32)	255 (45)	WNL
CPK (normal) (IU/liter)	850 (134)	145 (51)	ND	WNL	ND	192 (134)	ND	WNL
Complete blood count								
Hemoglobin (nadir) (grams/dl)	14.7	15.1	12	9.4	12.0	10.5	12	13.5
Leukocytes (on admission) (per cu mm)	36,800	33,900	20,000	10,400	11,000	14,400	8,700	15,300
Segmented neutrophils (%)	53	41	36	26	39	60	76	62
Bands (%)	23	55	56	70	22	38	15	23
Triglycerides (mg/dl)	ND	ND	ND	298 (155)	610 (175)	239 (155)	WNL	WNL
Albumin (normal) (grams/dl)	2.2 (3.5)	2.6 (3.5)	4.5 (3.5)	2.9 (3.5)	2.7 (3.5)	3.0 (3.4)	3.0 (3.5)	2.4 (3.5)
Calcium/phosphorus (mg/dl)	7.0/3.5	7.8/1.87	7.4/1.07	6.6/4.1	7.7/1.9	7.2/1.1	7.9/1.7	7.7/1.7
X-ray study of the chest	WNL	bilat. pleural effusion, ULN heart	interstitial infiltrates	hilar infiltrates esp. on left	diffuse bilat. interstitial infiltrates	WNL	WNL	WNL
Prothrombin time (control) (sec)	14.8 (10.5)	14 (11)	15 (11)	16 (12.5)	WNL	17 (11.5)	ND	16.9 (11.8)
Partial thromboplastin time (normal) (sec)	39 (<35)	45.5 (<35)	45 (<35)	44 (<40)	WNL	39 (<40)	ND	39.1 (<40)
Fibrinogen/fibrin split products	ND	440/>10<40	345/<10	275/neg	380/neg	540/neg	ND	445/neg
Platelet count (per cu mm)	186,000	84,000	59,200	93,000	67,000	145,000	106,000	115,000

BUN = blood urea nitrogen; CPK = creatine phosphokinase; ND = not determined; SGPT = serum alanine aminotransferase; ULN = upper limits of normal; WNL = within normal limits.

Summary of Toxic Shock Syndrome Cases

All eight cases of toxic shock syndrome that we saw followed the same general pattern. Patients were women (aged 16 to 40 years old) who became ill within two to four days of the onset of their menstrual periods. All patients were tampon users. Initially, patients visited their physicians, reporting fever, myalgia, sore throat, nausea, vomiting and diarrhea, and most were treated for pharyngitis or scarlet fever with penicillin. Some of the patients were thought to have urinary tract infections. Patients did not, however, respond to initial antibiotic therapy; they seemed to be in a toxic condition and were usually admitted to a hospital nearby.

Patients were usually referred after 24 to 48

hours in hospital because of either persistent or deteriorating signs and lack of a definite diagnosis. On referral, patients were critically ill, with hypotension, tachycardia and toxic appearance. All patients were strikingly red with a general flush, had some element of pharyngitis and had abdominal pain and tenderness. Table 2 summarizes the findings for all eight cases. Several patients had some noticeable injection of the conjunctiva; pronounced generalized tissue edema; scarlet fever rash (Figure 1), including sandpaper feel to the skin of the torso, circumoral pallor, strawberry tongue (Figure 2) and Pastia lines in skin folds; vaginitis, and foul-smelling vaginal discharge. All patients were lethargic and irritable although recent memory appeared intact. On being aroused, the patients had normal orientation.

Table 1 gives the laboratory findings for the eight patients. Generally, the serum creatinine level was elevated on admission to hospital and liver function abnormalities (including elevated levels of total and direct bilirubin, alkaline phosphatase and serum alanine aminotransferase [SGPT]) were evident. The complete blood count had characteristic neutrophilia with a pronounced shift to the left and toxic granulation. Several days after admission, the hemoglobin count usually became reduced in association with a low reticulocyte count. It usually returned to within normal limits by the time of discharge. Platelet count also dropped within two days of admission. This drop was not related to the presence of fibrin split products or depressed serum fibrinogen. Several patients did have slight prolongation of prothrombin time and partial thromboplastin time, but these changes were not associated with clinical bleeding. When measured, triglyceride levels were usually elevated. Serum albumin levels almost invariably were depressed on admission even though the patients had been ill only two or three days before entering the hospital. As noted in the Mayo Clinic case reports,[6] serum calcium values were depressed, although this was associated with low serum protein levels. Serum phosphorus levels

TABLE 2.—*Summary of Findings in Eight Patients With Toxic Shock Syndrome*

Finding	*Patient and Date of Case*							
	(1) 1977	*(2) 1978*	*(3) 1979*	*(4) 1979*	*(5) 1980*	*(6) 1980*	*(7) 1980*	*(8) 1980*
Temperature >38.9°C (102°F)	+	+	+	+	+	+	+	+
Rash								
Erythroderma	+	+	+	+	+	+	+	+
Scarlatiniform	..	+	+	..	+	+	−	+
Desquamation	+	+	+	+	+	+	+	+
Mucous membrane involvement								
Conjunctival suffusion	ND	+	+	−	+	+	+	+
Pharyngitis	+	+	+	+	+	+	+	+
Vaginitis	+	+	−	+	+	+	+	+
Shock								
Hypotension	+	+	+	+	+	+	+	+
Multisystem involvement								
Renal function abnormalities	+	+	+	+	+	+	+	+
Vomiting	+	+	+	+	+	+	+	+
Diarrhea	+	+	+	+	+	+	−	+
Liver function abnormalities	−	−	+	+	+	+	+	+
Myalgia	+	+	−	+	+	−	+	+
Neutrophilia	+	+	+	+	+	+	+	+
Platelet abnormalities								
<100,000 early	−	+	+	+	+	−	−	−
>400,000 7 days	ND	ND	ND	ND	+	+	+	ND
Cardiopulmonary	ARDS	MYO	ARDS	ARDS	ARDS	M HYP	−	M HYP
CNS changes	−	IRRIT	SOMN	IRRIT	DELIR	SOMN	CONF	−
Miscellaneous								
Staphylococcus cultured from vagina	+	ND	ND	+	−	−	+	+
Number of illnesses	1	2	1	3	1	1	1	1
Menses	+	+	+	+	+	+	+	+

ARDS = adult respiratory distress syndrome; CONF = confusion; CNS = central nervous system; DELIR = delirium; IRRIT = irritability; M HYP = minor hypoxia; MYO = myocarditis; ND = not determined; SOMN = somnolence.

were also low on admission. Pancreatitis was not clinically apparent in our patients, and patient 4 had normal serum amylase values. Blood gas determinations, when done soon after admission, showed a metabolic acidosis. The lactic acid level was measured in one patient and was abnormally elevated. In several patients the condition progressed to adult respiratory distress syndrome and hypoxia developed.

After admission to hospital, hypotension improved within 24 hours with supportive therapy. This was associated with a decrease in temperature. A spontaneous diuresis ensued followed by clearing of the diffuse interstitial edema, as indicated by x-ray studies of the chest. Improvement in generalized tissue edema became obvious and normal renal function returned. Patient 2 was the only patient in our series for whom signs of definite myocardial failure developed. This patient, in addition to electrocardiographic abnormalities, had enlargement of the heart, pulmonary edema, pleural effusion and gallop rhythm. These changes were slow to resolve, and this patient was ill longer than the others. For most patients, the characteristic desquamation of skin occurred during convalescence, usually about a week after onset of illness. The skin peeled mostly from the palms of the hands and the soles of the feet, but some scaling occurred on the torso as well.

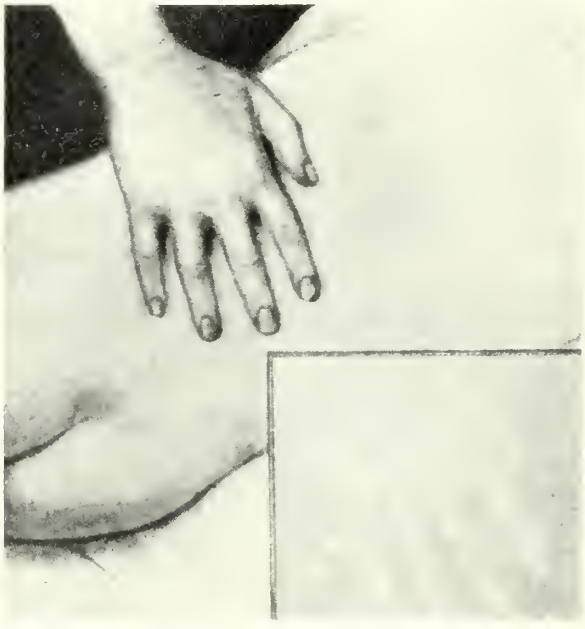


Figure 1.—Illustration of the blanching of scarlet fever rash. This appearance is similar in toxic shock syndrome. (Reproduced with permission from Dick GF, Dick GH: Scarlet Fever. Copyright © 1938 by Year Book Medical Publishers, Inc, Chicago.)

Figure 2.—Patient with toxic shock syndrome and strawberry tongue.

Table 3 outlines acute and convalescent titers obtained in diagnostic evaluation. In addition to the ones mentioned in Table 3, titers to Echo viruses 1, 3, 4, 6, 9, 14 and 19 and viral cultures done at Indiana University for one patient were negative. Antistreptolysin (ASO) titers less than or equal to 1:166 were stable in convalescence. Patient 5, whose ASO titer was 1:500 on admission, had been appropriately treated for a presumed group A *Streptococcus* infection two days before becoming critically ill with toxic shock syndrome. ASO titer was 1:250 when measured 11 days later. Hepatitis B antigen studies for two patients with pronounced liver function abnormalities gave negative results. Epstein-Barr virus titer was stable in one patient. Mononucleosis spot test, obtained for four patients, was negative.

Treatment

Four of our patients were treated with chloramphenicol, one with cephalothin and gentamicin, and one with ampicillin and gentamicin. The patients seen most recently were treated with nafcillin and the most recent one received a vinegar-water vaginal douche promptly on admission to the emergency room. Recovery usually began within 24 hours of admission to the regional hospital, and all patients completely recovered. However, we cannot say whether the antibiotic regimen had anything to do with patient improvement. Our impression is that the early treatment given most of our patients for presumed streptococcal pharyngitis (commonly penicillin) did not prevent severe complications. Antibiotic treatment given

by the time patients manifested severe toxic signs may have been unrelated to recovery. Possibly more important than antibiotic therapy was careful supportive care and fluid management to prevent the development of adult respiratory distress syndrome.

Discussion

The Center for Disease Control (CDC) considers a case definition of toxic shock syndrome to include all six of the following signs or symptoms:

1. Fever (temperature $\geq$38.9°C [102°F]).
2. Rash (diffuse macular erythroderma).
3. Desquamation, one to two weeks after onset of illness, particularly of palms and soles.
4. Hypotension (systolic blood pressure $\leq$90 mm of mercury for adults or lower than the fifth percentile by age for children younger than 16 years, or orthostatic syncope).
5. Involvement of at least four of the following organ systems:
   - Gastrointestinal (vomiting or diarrhea at onset of illness).
   - Muscular (severe myalgia or creatine phosphokinase level two times the upper limit of normal or greater).
   - Mucous membrane (vaginal, oropharyngeal or conjunctival hyperemia).
   - Renal (blood urea nitrogen or creatinine level at least twice the upper limit of normal or five or more leukocytes per high-power field—in the absence of a urinary tract infection).
   - Hepatic (total bilirubin, SGOT or SGPT twice the upper limit of normal or more).
   - Hematologic (platelets $\leq$100,000 per cu mm).
   - Central nervous system (disorientation or alterations in consciousness without focal neurological signs when fever and hypotension are absent).
6. Negative results on the following tests, if obtained:
   - Blood, throat or cerebrospinal fluid cultures.
   - Serological tests for Rocky Mountain spotted fever, leptospirosis or measles.

Toxic shock syndrome has been associated with positive vaginal cultures for *Staphylococcus aureus*,[4,5] but this was determined after our early cases were seen. Thus, in the early cases, either *S aureus* was not sought or vaginal specimens were not obtained for culturing. More recently, vaginal specimens have been cultured, although most patients had begun receiving antibiotics before the cultures were obtained. Therefore, only four of the eight cases in Table 2 had vaginal cultures that were positive for *S aureus*. Antibiotic sensitivity patterns for *S aureus* were the same on all four of these cultures. They were sensitive to cephalosporins, gentamicin, methicillin, erythromycin, clindamycin and tetracycline while resistant to ampicillin and penicillin.

Comparison of Kawasaki Disease With Toxic Shock Syndrome

Because of the striking similarities between adult Kawasaki disease and toxic shock syndrome, we examined the cases of adult Kawasaki disease

TABLE 3.—*Summary of Titers and Throat Cultures Obtained for Seven Patients With Toxic Shock Syndrome**

Finding	Patient (1)	(2)	(3)	(4)	(5)	(6)	(7)
Adenovirus	NS	TS	TS	NS	TS	TS	TS
Antinuclear antibodies	NS	neg	NS	neg	neg	neg	NS
Antisreptolysin O or streptozyme	1:166	neg	neg	neg	1:500	1:125	neg
Cytomegalovirus	NS	neg	NS	NS	neg	neg	neg
Herpes	NS	TS	TS	NS	NS	NS	NS
Leptospirosis	NS	neg	NS	NS	neg	neg	neg
Mycoplasma	NS	TS	NS	NS	TS	TS	neg
Rocky Mountain spotted fever	NS	NS	TS	NS	NS	neg	neg
Rubella	NS	TS	TS	NS	TS	TS	TS
Rubeola	NS	TS	TS	NS	neg	neg	TS
Throat cultures for group A strep (before antibiotic therapy)	NS	neg	neg	NS	NS	neg	neg
Toxoplasmosis	NS	neg	NS	NS	neg	neg	neg
Varicella	NS	TS	TS	NS	NS	NS	NS

neg = negative; NS = not sought; strep = *Streptococcus;* TS = titer stable

*Diagnostic titers obtained on patient 8 are still pending.

reported in the literature. A summary of our findings is given in Table 4. The reviewed cases could have been toxic shock syndrome instead of Kawasaki disease because all patients were female, were acutely ill and were frequently hypotensive, and most had a fever lasting less than five days. No menstrual history was given, although one patient's illness recurred after a four-week interval. By definition, Kawasaki disease occurs in children younger than 10 years of age and involves cervical adenopathy and a fever lasting more than five days.[13-20] Thromboeytopenia and hypotension are not characteristic of Kawasaki disease. Kawasaki rash has a distinct appearance, being more macular-papular. Coronary aneurysms found in fatal cases of Kawasaki disease have not yet been observed in toxic shock cases. However, Todd indicates a coronary vasculitis may be present in patients with toxic shock syndrome (written communication, James Todd, MD, Children's Hospital, Denver, Colorado, December 5, 1979).

Literature Search

Toxic shock syndrome has been described in menstruating women and has been associated with tampon use.[2-5] A CDC study reported 95 percent of 55 cases had involved menstruating women and most had been tampon users.[4] A follow-up CDC study showed that "50 of 50 cases with onset during menstruation (100 percent) used tampons as compared to 43 of 50 controls (86 percent) ($P=0.02$ by McNemar test with continuity correction)."[5]

Tampons, especially the newer superabsorbent ones, have been found to cause definite changes in the vaginal mucosa,[22] but whether those changes are related to toxic shock syndrome has not been determined.

Recent data on a significantly increased incidence (71 percent) in women using Rely tampons resulted in the removal of this product from the market.[21] Of six of our cases where brand was known, three patients used Rely. Although removal of Rely tampons from the market may result in some reduction of cases, this would not be expected to eliminate all incidence of the disease. Indeed, we have seen one case of toxic shock syndrome since Rely was taken off the market.

Toxic shock syndrome has not been associated with birth control method, history of herpes infections, or use of sprays or douches.[5]

Staphylococcus aureus was present in 43 of 44 vaginal cultures taken from patients with toxic shock syndrome, when cultures were obtained before initiating antibiotic therapy.[3,21] *Staphylococcus aureus* is normally carried in the vaginas of

TABLE 4.—*Summary of Findings in Adult Kawasaki Disease Cases Reported in the Literature*

	Snell[7] *1980*	*Caron*[8] *1980*	*Everett*[9] *1979*	*Everett*[9] *1979*	*Everett*[9] *1979*	*Milgrom*[10] *1980*	*Schlossberg*[11] *1977*	*Lee*[12] *1978*
Fever	+	+	+	+	+	+	+	+
Rash								
Erythroderma	+	+	+	+	+	+	+	+
Scarlatiniform	−	+	..	+	..	..	+	..
Desquamation	+	+	+	+	+	+	+	+
Mucous membrane involvement								
Conjunctival suffusion	NM	−	+	+	+	+	+	+
Pharyngitis	+	+	+	+	+	−	+	+
Vaginitis	NM	NM	NM	NM	NM	−	+	−
Shock								
Hypotension	+	−	NM	+	+	+	−	−
Multisystem involvement								
Renal function abnormalities	+	NM	NM	+	+	+	+	+
Vomiting	+	+	NM	+	−	+	−	−
Diarrhea	−	−	NM	+	+	−	+	+
Liver function abnormalities	+	+	NM	NM	−	+	+	+
Myalgia or elevated CPK	+	NM	−	+	−	+	+	−
Neutrophilia	+	+	+	+	+	+	+	+
Cardiopulmonary	−	NM	−	−	−	−	−	−
CNS changes	NM	+	NM	NM	NM	+	−	−
Miscellaneous								
Staphylococcus cultured	+	NM	NM	NM	NM	NM	+	NM
Number of illnesses	3	1	1	1	1	2	1	1
Menses	+	NM	NM	NM	NM	NM	NM	NM
Cervical lymph nodes	+	+	+	1-1.5 cm	1.5 cm	−	0.5 cm	1-2 cm

CPK = creatine phosphokinase; CNS = central nervous system; NM = not mentioned.

2 percent to 15 percent of the female population.[23,24] A CDC study[21] isolated *S aureus* from 4 of 55 unmatched control women who visited family planning clinics during their menstrual periods. In a University of Utah study, a similar percentage of vaginal cultures taken during women's normal menstruation grew *S aureus* (personal communication, Charles Smith, MD, University of Utah Medical Center, September 8, 1980). Phage type is known to vary.[5]

Todd and co-workers[1] thought that the toxin produced by *S aureus* in toxic shock syndrome in children was similar to, but distinct from, the one produced in scalded skin syndrome. An association is still being evaluated. Staphylococcal infections were previously described as simulating scarlet fever.[25-27] A toxin from *Staphylococcus* organisms is also being evaluated in animals for ability to reproduce this syndrome.[28]

Also unknown is the association of toxic shock syndrome in women and Kawasaki disease in children, although the incidence of both syndromes is increasing. Both syndromes have similar signs and symptoms, but they affect different age groups.[4,5,13-18] Also, toxic shock syndrome is an acute illness associated with hypotension while Kawasaki disease is not.[29] The presence of toxic shock syndrome in a community has not been reported to be associated with Kawasaki disease, but similarity in the syndromes cannot be ignored and may be of significance.

Differential Diagnosis

Streptococcal scarlet fever should be ruled out because of its striking similarity at onset to toxic shock syndrome. Other causes that should be considered are Epstein-Barr virus,[30] rubeola, leptospirosis, Rocky Mountain spotted fever,[17] Stevens-Johnson syndrome and acute collagen disease.[4,14]

Treatment

Most authorities recommend antistaphylococcal treatment because *S aureus* has been found in vaginal cultures taken from untreated patients with toxic shock syndrome and because toxic shock syndrome has been known to be clinically similar to recognized staphylococcal syndromes.[1-3,5] In our experience, penicillin was not effective therapy. Penicillinase-resistant drugs have not been known to ameliorate the disease but have appeared to reduce recurrences.[5] Cultures of the nares, stool, pharynx, vagina, blood, cervix and any other infection site should be obtained before beginning antibiotic therapy.[5] Fluid management is important. Patients appear to have diffuse capillary leakage, with generalized tissue edema and associated hypotension. Once renal perfusion and hypotension have improved, fluids should be reduced to decrease the potential for adult respiratory distress syndrome. Patients appear to have a spontaneous diuresis once toxic effects have reversed.

The CDC advises against tampon use for several cycles in patients who have had this syndrome because the syndrome frequently recurs in subsequent menstrual periods.[5] If *S aureus* has been found in the vagina, tampons should probably not be used until the organism has been eradicated.[5] Patients may reduce the risk by not wearing tampons continuously throughout their menstrual cycles.[5] Whether the critical illness associated with the syndrome can be prevented by antistaphylococcal treatment early in presentation has not been determined.

Cases should be reported to the local state health department or to the CDC, Division of Special Pathogens.[5] If possible, serum specimens from patients during acute and convalescent stages of illness should be obtained and *S aureus* cultures saved for future investigation.

Conclusions

The authors are not aware of any published cases of toxic shock syndrome in menstruating women before 1975. Cases appear to be increasing,[21] although this increase may be partially related to improved recognition by physicians. The association of the syndrome with menstruating women and tampons is very clear. Vaginal *S aureus* has been incriminated. Most tampon manufacturers recently have developed new superabsorbent tampons, but whether this change is related to the seeming increase in the incidence of toxic shock syndrome or whether there has been a change in the nature of *S aureus* remains speculation.

REFERENCES

1. Todd J, Fishaut M, Kapral F, et al: Toxic-shock syndrome associated with phage-group-I staphylococci. Lancet 2:1116-1118, Nov 25, 1978

2. Schrock CG: Disease alert. JAMA 243:1231, Mar 28, 1980

3. State of Utah Communicable Disease Newsletter: Staphylococcal toxic-shock syndrome. Feb 1980

4. Toxic-shock syndrome—United States. Morbidity Mortality Weekly Rep 29:229-230, May 23, 1980

5. Follow-up toxic-shock syndrome—United States. Morbidity Mortality Weekly Rep 29:297-299, Jun 27, 1980

6. McKenna UG, Meadows JA, Brewer NS, et al: Toxic-shock syndrome, a newly recognized disease entity. Mayo Clin Prac 55: 663-672, Nov 1980

7. Snell GF: Adult Kawasaki disease—Three occurrences in the same patient (Correspondence). West J Med 132:548-549, Jun 1980

8. Caron GA: Kawasaki disease in an adult. JAMA 243:430, Feb 1, 1980

9. Everett ED: Mucocutaneous lymph node syndrome (Kawasaki disease) in adults. JAMA 242:542-543, Aug 10, 1979

10. Milgrom H, Palmer EL, Slovin SF, et al: Kawasaki disease in a healthy young adult. Ann Intern Med 92:467-470, Apr 1980

11. Schlossberg D, Kandra J, Kreiser J: Possible Kawasaki disease in a 20-year-old woman. Arch Dermatol 115:1435-1436, Dec 1979

12. Lee TJ, Vaughan D: Mucocutaneous lymph node syndrome in a young adult. Arch Intern Med 139:104-105, Jan 1979

13. Kawasaki T, Kosaki F, Okawa S, et al: A new infantile acute febrile mucocutaneous lymph node syndrome (MLNS) prevailing in Japan. Pediatrics 54:271-276, Sep 1974

14. Kahn G: Mucocutaneous lymph node syndrome (Kawasaki's disease). Arch Dermatol 114:948-950, Jun 1978

15. Morens DM, Anderson LJ, Hurwitz ES: National surveillance of Kawasaki disease. Pediatrics 65:21-25, Jan 1980

16. Morens DM, O'Brien RJ: Kawasaki disease in the United States. J Infect Dis 137:91-92, Jan 1978

17. Bergeson PS, Schoenike SL: Mucocutaneous lymph node syndrome—A case masquerading as Rocky Mountain spotted fever. JAMA 237:2299-3002, May 23, 1977

18. Riley HD: Mucocutaneous lymph node syndrome (Kawasaki disease). J Infect Dis 134:302-305, Sep 1976

19. Lauer BA, Bruhn FW, Todd JK, et al: Mucocutaneous lymph node syndrome in Denver. Am J Dis Child 130:610-612, Jun 1976

20. Terezhalmy GT: Mucocutaneous lymph node syndrome. Oral Surg 47:26-30, Jan 1979

21. Center for Disease Control: Follow-up on toxic-shock syndrome. Morbidity Mortality Weekly Rep 29:441-445, Sep 19, 1980

22. Friedrich EG, Siegesmund KA: Tampon-associated vaginal ulcerations. Obstet Gynecol 55:149-156, Jan 1979

23. Hoeprich PD (Ed): Indigenous microbiota of the genital tract table, section X, *In* Infectious Diseases, 2nd Ed. Hagerstown, MD, Harper and Row Publishers, 1977, p 480

24. Bartlett JG, Onderdonk AB, Drude E, et al: Quantitive bacteriology of the vaginal flora. J Infect Dis 136:271-277 Aug 1977

25. Aranow H, Wood WB: Staphylococcic infection simulating scarlet fever. JAMA 119:1491-1495, Aug 29, 1942

26. Feldman CA: Staphylococcal scarlet fever. N Engl J Med 267:877-878, Oct 26, 1962

27. McCloskey RV: Scarlet fever and necrotizing fasciitis caused by coagulase-positive hemolytic *Staphylococcus aureus*, phage-type 85. Ann Intern Med 78:85-87, Jan 1973

28. Schlievert PM, Schoettle DJ, Watson DW: Purification and physiochemical and biological characterization of a staphylococcal pyrogenic exotoxin. Infect Immun 23:609-717, Mar 1979

29. Todd JK: Mucocutaneous lymph node syndrome (Kawasaki disease) in adults. JAMA 243:631, Apr 25, 1980

30. Barbour AG, Krueger GG, Feorino PM, et al: Kawasaki-like disease in a young adult. JAMA 241:397-398, 1979

Refer to: Forrest JV, Friedman PJ: Radiologic errors in patients with lung cancer. West J Med 134:485-490, Jun 1981

Radiologic Errors in Patients With Lung Cancer

JOHN V. FORREST, MD, *and* PAUL J. FRIEDMAN, MD, *San Diego*

Some 20 percent to 50 percent of detectable malignant lesions are missed or misdiagnosed at the time of their first radiologic appearance. These errors can result in delayed diagnosis and treatment, which may affect a patient's survival. Use of moderately high (130 to 150) kilovolt peak films, awareness of portions of the lung where lesions are often missed (such as lung apices and paramediastinal and hilar areas), careful comparison of current roentgenograms with those taken previously and the use of an independent second observer can help to minimize the rate of radiologic diagnostic errors in patients with lung cancer.

A RATE OF radiologic diagnostic error of 20 percent to 50 percent has been well documented in previous years.[1-5] This study analyzes the factors that led to such errors in 27 cases of lung cancer. Reasons for these errors and methods to improve the detection rate are suggested.

Patients and Methods

A retrospective series was collected of consecutively seen patients in whom lung cancer had been diagnosed. Of these, 78 patients had a radiologically apparent mass. Current and previous chest roentgenograms and reports on these patients were reviewed. In eight cases, radiologic errors in diagnosis had been made before confirmation of the disease.

Over a subsequent two years roentgenograms of the chest of all patients with newly or previously diagnosed lung cancer were checked for radiologic error. Of the 143 cases of lung cancer diagnosed, 19 errors were found.

The 27 cases of radiologic error were reviewed by a second radiologist. He concurred that in all cases there had been an error in detection or interpretation but that no case in which the diagnosis was possible only in retrospect had been included. Questionable cases were not classified as radiologic errors.

Medical records of the 27 patients in whom lung cancer had been missed radiologically were reviewed to determine the length of time between the error and accurate diagnosis. These records were also analyzed to establish if the radiologic error had an effect on eventual surgical management of the tumor.

Results

The 27 radiologic errors involved 22 cases in which the abnormality had been missed, 4 in which radiologic findings were reported but misinterpreted and 1 case in which there were errors in both detection and interpretation at different times (Table 1). Therefore, in 23 cases there was a delay in diagnosis of lung cancer because of a failure to detect a significant radiologic finding.

The location of each radiologically apparent lesion on posteroanterior or lateral roentgenograms was plotted on a diagram of the chest for

From the Department of Radiology, University of California, San Diego, School of Medicine.

Submitted, revised, December 15, 1980.

Reprint requests to: John V. Forrest, MD, Department of Radiology, University of California Medical Center, 225 Dickinson St., San Diego, CA 92103.

TABLE 1.—*Radiologic Errors in Lung Cancer Diagnosis*

Missed observations	22
Misinterpreted findings	4
Both missed and misinterpreted (at different times)	1
TOTAL	27

TABLE 2.—*Analysis of Consecutive Cases of Lung Cancer in Which There Was a Radiologically Apparent Mass*

Total cases included	78
Previous films available for comparison	20
Observation missed	7
Finding misinterpreted	1
Rate of diagnostic error	40%

the 78 consecutive cases of lung cancer, group 1 (Figure 1), and for the 23 patients in whom there had been a radiologic error in diagnosis of lung cancer, group 2 (Figure 2).

Of the 78 patients in group 1, there were 20 for whom previous roentgenograms were available for comparison. Radiologic errors had been made in reading earlier films of eight patients in this group (Table 2).

When all previous roentgenograms were reviewed in the 23 patients in group 2 (failure of detection), multiple errors were discovered in most cases (Table 3).

The diagnosis of lung cancer was often delayed months to years after the first definite radiologic evidence of a mass had gone unrecognized (Table 4). This delay in diagnosis may have affected patients' chances for surgical cure (Table 5).

Discussion

Error in diagnostic radiology has been studied by many authors, all of whom have concluded that a large number of significant abnormalities is

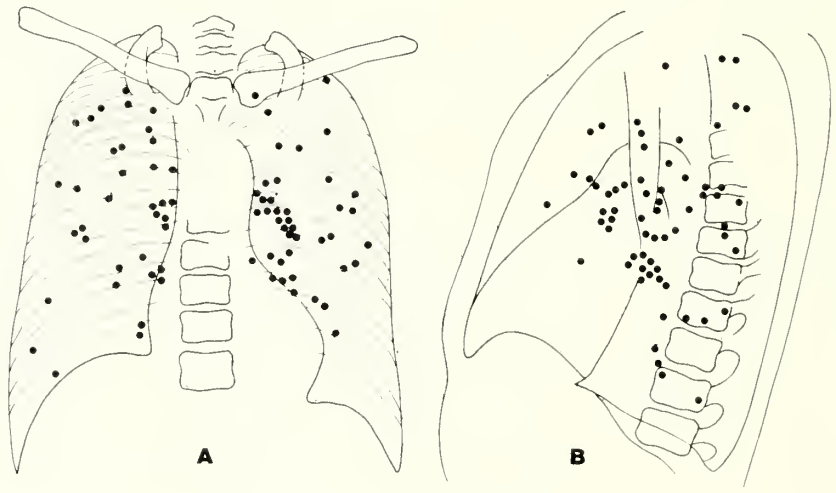


Figure 1.—A, Posteroanterior diagram of the chest with the locations of malignant lesions in 78 consecutively seen cases of lung cancer. (Reproduced by permission from Forrest and Sagel[20]; copyright 1979 by the Radiological Society of North America, Incorporated.) **B,** Lateral diagram of the chest with the locations of the lesions in 78 consecutively seen cases of lung cancer.

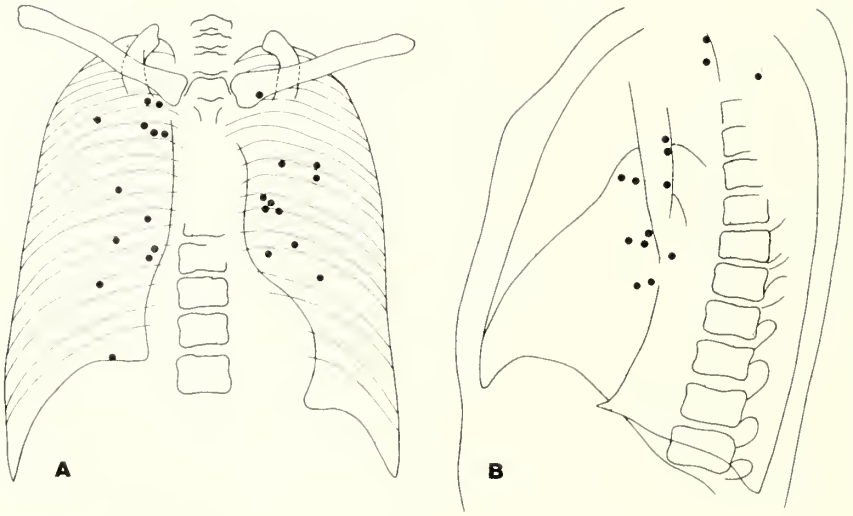


Figure 2.—A, Posteroanterior diagram of the chest with the locations of 23 missed lung cancer lesions. **B,** Lateral diagram of the chest with the locations of 23 missed cases of lung cancer. Note the predominance of central and apical lesions in both views.

TABLE 3.—*Missed Observations*

On one radiologic study	10
On two radiologic studies	5
On three or more radiologic studies	8
TOTAL	23

TABLE 4.—*Delay in Diagnosis Because of Error*

Delay (months)	*No. of Cases*	*Delay (months)*	*No. of Cases*
0-1	6	12-24	3
2-3	3	24-36	2
3-6	3	36-48	2
6-12	8		
		TOTAL	27

TABLE 5.—*Effect of Error on Patient Management*

Number of patients	27
Delayed resection that was still possible later	8
Unresectable but might have been resectable at time of error	3

either not detected, not reported or misinterpreted. Estimates of error rate have varied from 20 percent to 50 percent.[1-5] Among the 78 consecutive cases of lung cancer in which there was a radiologically apparent mass, 20 had previous films for comparison. In 8 of the 20 patients the mass was obviously present on review of earlier examinations but either had been missed (7 cases) or misinterpreted (1 case). The false-negative error rate of 40 percent in this small series is in line with the findings of others. It should be emphasized that only a clearly detectable lesion has been classified as a miss. Questionable or very small lesions visible only in retrospect were not considered errors for this report.

Survival after operations to remove small malignant nodules is high.[6] Resectability rates are higher in patients in whom lung cancer is found in a regular screening program.[7,8] Rigler and coworkers[4] have reemphasized that many peripheral neoplasms grow very slowly and are demonstrable on roentgenograms for a long time before they show evidence of unresectability because of local invasion or distant spread. Although most physicians dealing with patients with lung cancer have assumed that early diagnosis and surgical procedures lead to improved survival, the report of the Philadelphia Pulmonary Neoplasms Research Project did not support this premise.[9] It was found that radiologic screening for early detection of lung cancer did not significantly enhance average survival. However, the project relied on photofluorograms, on which small lesions are hard to detect.[9] Several other major studies have reached opposite conclusions.[6-8,10-12] Overall, the balance of evidence supports the position that early radiologic detection of lung cancer is useful in increasing both surgical resectability rates and survival.

The effects of diagnostic errors on ultimate outcome are hard to determine. In many of the patients the radiologic error led to a significant delay in establishing the diagnosis of lung cancer (Table 4). In 15 of the 27 patients the time from first radiologic appearance to diagnosis was longer than six months and in two instances it was more than three years. Many of the tumors would have been unresectable even when first seen on the roentgenograms because of their location or, more commonly, because of coexisting disease, particularly severe emphysema. Given these considerations, it was concluded that 11 of the 27 patients had reduced chances of surgical cure because of the delay in diagnosis (Table 5).

Factors contributing to radiologic error are complex and hard to isolate. An inexperienced observer has a higher error rate than a radiologist[1]; however, Herman and Hessel[13] found that residents with a year of training had approximately the same likelihood of detecting abnormalities as fully trained radiologists. Garland[1] suggested that radiologists who subspecialized were less apt to make significant errors in their field. Errors in radiologic detection are more frequent if the reader is busy or rushed,[3] but fatigue does not appear to have this effect.[14,15] The rate of missed findings by radiologists working late in the day or after hours does not appear to increase.[3,14]

Lack of clinical correlation is a cause of error, particularly in trauma radiology.[3] Failure to study old reports and previous films carefully will also lead to error.[3] There were previous films available showing no abnormalities in 17 of the 23 cases involving detection errors; comparison clearly showed interval changes or new appearance of a shadow (Figures 3 and 4).

Although an inadequate or suboptimal examination can certainly cause a lesion to be missed, this was not a factor in our study. Several patients for whom films were of poor quality had other studies which clearly showed the abnormality. We regularly use a moderately high kilovolt peak (kVp) (130 to 150) which precludes underpenetration as a problem. In several cases a lighter film would have

shown a missed lesion better, but in no instance was a bright light necessary to see the abnormality. Other investigators have also concluded that technique plays a relatively unimportant role in the high rate of radiologic errors.[3]

Changing the technical factors of a roentgenogram and manipulating the image have been attempted to enhance the visibility of small lesions, particularly pulmonary nodules, to decrease the error rate.[16] The success of these attempts was questionable at best. Rigler[17] worked extensively with manipulation of the image by a television system, but this technique has not yet been shown to be of practical value. The use of 350 kVp films can increase the perceptibility of nodules.[18] However, the cost or inconvenience of new equipment, the loss of other information on the film and unfamiliarity with this technique have not yet led to its general acceptance.

The use of a kVp in the 130 to 150 range increases the availability of information from the parts of the lung overlying the mediastinum, hila and bones. Adequate penetration of these normal obscuring structures enhances the detectability of lesions. However, these regions were still the sites of most of the lesions missed in this study. The difference in distribution of lesions between the 78 consecutive cases of lung cancer and the 23

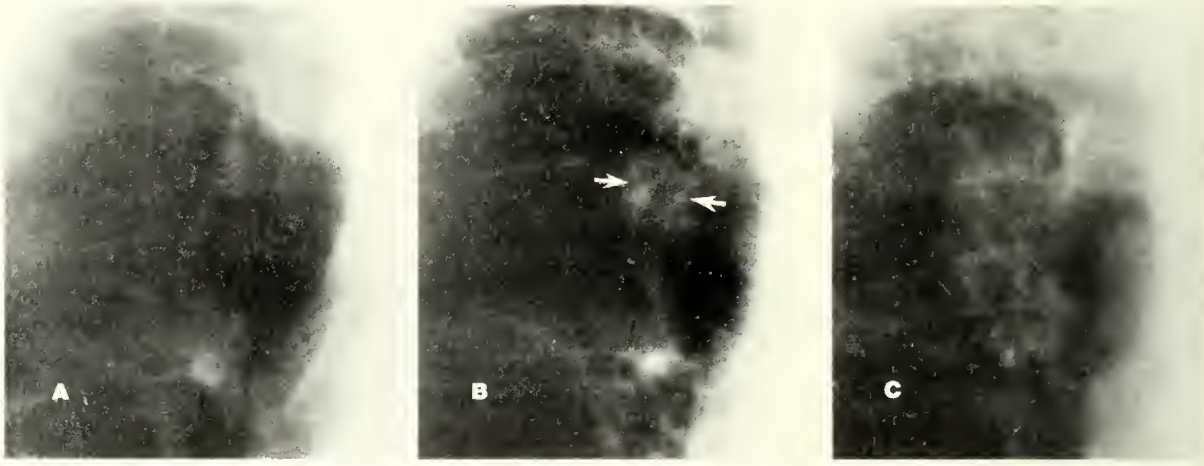


Figure 3.—A, Posteroanterior roentgenogram of right upper lung field. **B**, Growing mass (**arrows**) 16 months later, not reported. **C**, A year later, the mass is larger. Squamous cell carcinoma was found on needle aspiration of the lung.

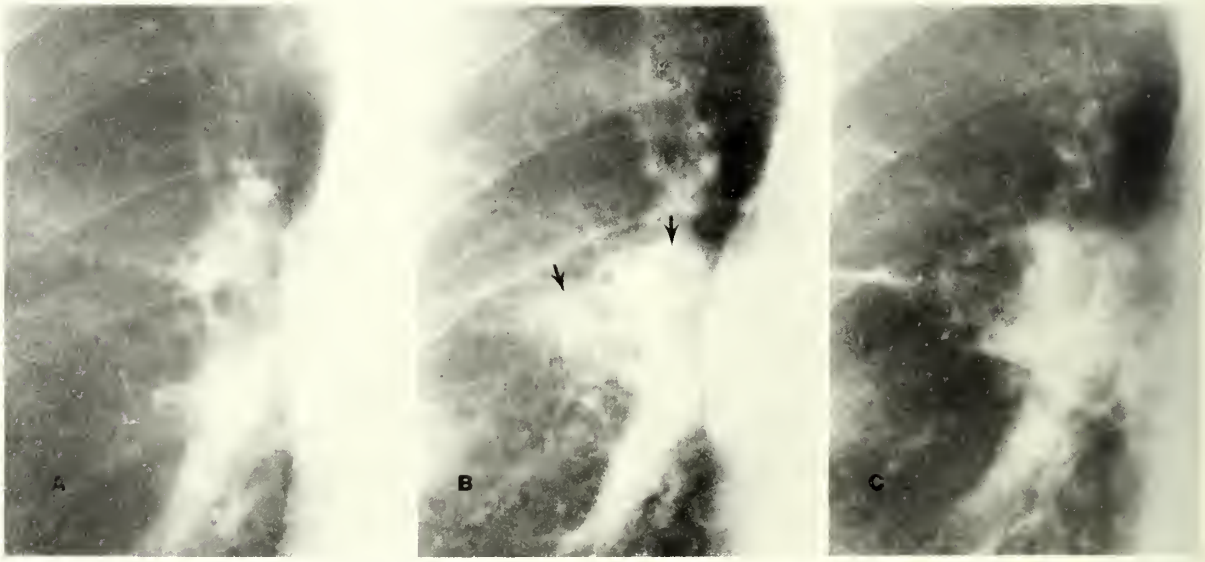


Figure 4.—A, Posteroanterior roentgenogram of right hilar area. **B**, Growing mass 14 months later lateral to and in superior pole of hilum (**arrows**) was missed. **C**, Larger mass five months later proved to be adenocarcinoma by bronchoscopic biopsy.

cases of missed lung cancer is striking (Figures 1 and 2). Most of the missed tumors occurred in the apices (especially the right) (Figure 3) and paramediastinal and hilar areas (Figure 4). Difficulty in separating normal structures from early lung cancer was the apparent cause of these errors.

At the right apex, posterior and anterior ribs (particularly the first costochondral junction), the clavicle, manubrium, innominate artery, lung vessels, apical capping and scars of previous granulomatous disease create a conglomeration of shadows that can readily obscure a small lesion. Variations in hilar and mediastinal density and contour are endless and allow early abnormalities to be overlooked. Experience and knowledge of normal anatomy should help in the search for these lesions, although many were missed by senior radiologists (and presumably by the senior clinicians at our medical center who often look at their patients' films). Knowledge of recent studies of normal radiologic mediastinal and hilar anatomy should help in the search for subtle abnormalities.[19]

Although the use of lateral chest films is critical for confirmation and localization of lung cancer, it was not a major factor in early diagnosis or error in our series. Two of the missed lesions (of those listed in Table 1) could be seen better in the lateral view. And in only two of the 78 consecutive cases of lung cancer could the lesions be seen better in the lateral films. However, no lesion in either group was visible only on the lateral roentgenogram. The lateral view complements the frontal film, especially for visualization of the lung bases and retrosternal space; however, very few of the cases of lung cancer developed in these regions (Figure 4). In a previous exensive evaluation of the value of lateral roentgenograms, no cases of cancer were discovered that could be seen only from this view.[20] On the other hand, in the group of missed lesions, 9 of 23 were visible only in the frontal projection.

In 5 of the 27 undiagnosed malignant lesions of the lungs, the error was due to misinterpretation of an observed abnormality. In one instance a large mediastinal mass was thought to be an aortic aneurysm. Another instance of lung cancer was interpreted as an enlarging left pulmonary artery. The other three cases involved slowly growing, poorly defined peripheral lesions, which were interpreted as chronic pneumonia. Misinterpretation due to slow tumor growth is significant because it delays treatment of the lesions most likely to be successfully managed surgically. In this series alveolar cell carcinoma was likely to be a misdiagnosed, slowly growing peripheral lesion.

Past studies have shown that an excellent way to reduce error is double reading.[2,3,21,22] Approximately half of significant errors can be avoided by this procedure.[2,3] Most of our roentgenograms were seen by a resident and a staff radiologist before being reported. In addition, many films were reviewed by specialists on the clinical services. Nevertheless, 13 of 23 cases of lung cancer were undetected on two or more studies (Table 3). Independent double reading by radiologists is impractical in many departments. A more immediate solution would be to teach technologists to screen films. Technologists were successfully trained to pick out lung cancer in the New York Early Lung Cancer Detection Program.[23] Sheft and his associates[24] also showed that specially trained technologists could accurately screen chest roentgenograms.

An error rate of about 30 percent appears to be an unavoidable aspect of chest radiology as it is currently practiced. With the recent rise in malpractice suits, many radiologists and nonradiologists are being sued for missing or misinterpreting a shadow caused by lung cancer. This legal challenge is inconsistent with the known limitations of accuracy of interpretation of chest films, as illustrated once again in this series. If a substantial rate of error in detection is a customary aspect of radiology, then such an error cannot be a justification for a liability action.

Another significant cause of mismanagement of patients with lung cancer occurs despite correct radiologic interpretation. In our review of records of patients with lung cancer, we found several instances in which a report suggesting the diagnosis was not read or was ignored by the referring physician. Even more frequently, patients missed follow-up appointments or refused further evaluation.

Conclusions

This retrospective study supports the observation that many detectable malignant lesions of the lung are missed at the time of their first radiologic presentation. Because all published studies confirm the high rate of error, it is suggested that such errors in diagnosis should not result in legal liabil-

ity. Unfortunately, these errors often result in a significant delay in diagnosis and treatment, which may affect resectability and, thereby, decrease the survival rate.

Use of moderately high (130 to 150) kVp is a practical technique which can increase the detection of lung cancer in several regions in which it is missed; these are the lung apices and paramediastinal and hilar areas. Awareness of the likelihood of error and careful checking of these problem areas on roentgenograms should help radiologists improve the detection rate of lung cancer.

The one proved method of reducing the error rate in the diagnosis of lung cancer is the use of a second independent observer. A trained radiologic technologist or the referring physician may be the most appropriate person for this role, in cooperation with the responsible radiologist. However, over 90 percent of our errors involved cases in which roentgenograms were reviewed by more than one radiologist; therefore, merely having a second trained observer does not eliminate many instances of missed lesions. Current radiologic techniques and practice still result in a high rate of error in the early diagnosis of lung cancer.

REFERENCES

1. Garland LH: Studies on the accuracy of diagnostic procedures. Am J Roentgenol Radium Ther Nucl Med 82:25-38, 1959

2. Groth-Peterson E, Lovgreen A, Thillemann J: On the reliability of the reading of photofluorograms and the value of dual reading. Acta Tuberc Scandinav 26:13-37, 1952

3. Smith MJ: Error and Variation in Diagnostic Radiology. Springfield IL, Charles C Thomas, 1967

4. Rigler LG, O'Loughlin BJ, Tucker RC: The duration of carcinoma of the lung. Dis Chest 23:50-71, 1953

5. Veeze P: Rationale and Methods of Early Detection in Lung Cancer. Netherlands, Van Gorcum and Co, 1968

6. Ray JF, Lawton BR, Magnin GE, et al: The coin lesion story: Update 1976. Chest 70:332-336, 1976

7. Stitik FP, Tockman MS: Radiographic screening in the early detection of lung cancer. Radiol Clin North Am 16:347-366, 1978

8. Cooperative Study Group for Early Detection of Lung Cancer in the German Democratic Republic: Roentgenographic chest screening in the detection and survival of patients with lung cancer. Ann Thorac Surg 26:406-412, 1978

9. Boucot KR, Weiss W: Is curable lung cancer detected by semiannual screening? JAMA 224:1361-1365, 1973

10. Jackman RJ, Good CA, Clagett OT, et al: Survival rates in peripheral bronchogenic carcinomas up to four centimeters in diameter presenting as solitary pulmonary nodules. J Thorac Cardiovasc Surg 57:1-8, 1969

11. Brett GZ: Earlier diagnosis and survival in lung cancer. Br Med J 4:260-262, 1969

12. Higgins GA, Shields TW, Keehn RJ: The solitary pulmonary nodule—Ten-year follow-up of Veterans Administration-Armed Forces Cooperative Study. Arch Surg 110:570-575, 1975

13. Herman PG, Hessel SJ: Accuracy and its relationship to experience in the interpretation of chest radiographs. Invest Radiol 10:62-67, 1975

14. Christensen EE, Dietz GW, Murry RC, et al: The effect of fatigue on resident performance. Radiology 125:103-105, 1977

15. Brogdon BG, Kelsey CA, Moseley RD: Effect of fatigue and alcohol on observer perception. AJR 130:971-974, 1978

16. Kundel HL, Revesz G: The influence of film density on the radiologic detection of lung lesions. Invest Radiol 12:199-200, 1977

17. Rigler LG: The Fleischner Memorial Lecture. Presented at Fleischner Society Postgraduate Course on Chest Radiology, Williamsburg, Va., March 1971

18. Christensen EE, Dietz GW, Murry RC, et al: Effect of kilovoltage on detectability of pulmonary nodules in a chest phantom. AJR 128:789-793, 1977

19. Heitzman ER: The Mediastinum. St. Louis, C.V. Mosby Co., 1977

20. Forrest JV, Sagel SS: The lateral radiograph for early diagnosis of lung cancer. Radiology 131:309-310, 1979

21. Hessel SJ, Herman PG, Swensson RG: Improving performance by multiple interpretations of chest radiographs: Effectiveness and cost. Radiology 127:589-594, 1978

22. Yerushalmy J: The statistical assessment of the variability in observer perception and description of roentgenographic pulmonary shadows. Radiol Clin North Am 7:381-392, 1969

23. Flehinger BJ, Melamed MR, Heelan RT, et al: Accuracy of chest film screening by technologists in the New York Early Lung Cancer Detection Program. AJR 131:593-597, 1978

24. Sheft DJ, Jones MD, Brown RF, et al: Screening of chest roentgenograms by advanced roentgen technologists. Radiology 94:427-429, 1970

Refer to: Krebber HJ, Szarnicki RJ, Hill JD: Preoperative management of proximal lesions of the left coronary artery system: Surgical implications. West J Med 134: 491-495, Jun 1981

Preoperative Management of Proximal Lesions of the Left Coronary Artery System: Surgical Implications

HANS J. KREBBER, MD; ROBERT J. SZARNICKI, MD, *and*
J. DONALD HILL, MD, *San Francisco*

Between January 1975 and December 1978, a total of 67 consecutive patients with left main coronary disease had coronary bypass operations at Pacific Medical Center in San Francisco. Of these, 54 were men and 13 women. The mean age was 59 years (range 44 to 77 years). Three groups were identified retrospectively. Sex ratio, age, symptoms, and coronary pathology and hemodynamics were comparable in all groups. Group 1 (24 patients) received no propranolol or had it discontinued at least two weeks preoperatively. Group 2 (28 patients) received propranolol up until two days before the operation. Group 3 (15 patients) received propranolol until the morning of the bypass operation. The overall mortality was 2.9 percent (2 patients). In Group 1, 33 percent (8 patients) had unstable angina preoperatively, while 50 percent (14 patients) in group 2 and 40 percent (6 patients) in group 3 had unstable angina. Perioperative infarction occurred in 12.5 percent (3 patients) in group 1, 25 percent (7 patients) in group 2 and 13 percent (2 patients) in group 3. Creatine phosphokinase myocardial band fractions in the postoperative period were lowest in group 3 but were notably elevated in group 2. Postoperative inotropic support was required in one patient (4 percent) in group 1, four patients (14 percent) in group 2, while none required support in group 3. The decreased incidence of perioperative infarction and reduced need for postoperative inotropic support in group 3 suggests that if propranolol is to be part of the pharmacological preoperative regimen, it can and should be continued up to the time of operation. Propranolol should not be discontinued in the immediate preoperative period.

Stenosis of the left main coronary artery, whether it involves the left coronary artery alone or is in combination with lesions of the right coronary artery, has been previously reported to carry a higher incidence of perioperative myocardial infarction as well as a higher perioperative mortality than lesions involving more peripheral vessels.[1] Myocardial revascularization for this

From the Department of Cardiovascular Surgery, Pacific Medical Center, San Francisco.

Submitted, revised, December 1, 1980.

Reprint requests to: Robert J. Szarnicki, MD, Pacific Medical Center, P.O. Box 7999, Annex Suite 326, San Francisco, CA 94120.

ABBREVIATIONS USED IN TEXT

CPK-MB = creatine phosphokinase-myocardial band (fraction)
EF = ejection fraction
EKG = electrocardiogram
LMCAD = left main coronary artery disease

small subgroup of patients has been shown to be effective in relieving symptoms as well as increasing longevity when compared with the results of medical therapy.[2] The use of propranolol (Inderal) as a β-adrenergic blocking agent has become an increasingly important addition to the armamentarium of physicians responsible for the medical management of these patients. Its use, however, has remained somewhat controversial because its effectiveness is limited in patients with depressed myocardial function and in those with bronchospastic pulmonary disease.[4] In these patients its use is contraindicated. Earlier reports have suggested that a severe postoperative low cardiac output syndrome and bradyarrhythmias were caused by the preoperative use of propranolol.[5] Sudden cessation of propranolol during the preoperative period has been reported to result in a "withdrawal syndrome," with aggravation of symptoms leading to progressively unstable angina and, in some instances, acute myocardial infarction.[6,7] Acute myocardial infaretion, in combination with left main stem lesions, is associated with an extremely high mortality,[8,9] and several groups have advocated the use of elective intra-aortic balloon counter pulsation during the immediate preoperative period.[10,11] With the judicious use of β-blocking agents and improvement in anesthetic induction techniques the need for the intra-aortic balloon has become less frequent and is often replaced by pharmacological afterload reduction. It is now recommended only in those patients unresponsive to maximum medical therapy.

TABLE 1.—*Sex and Age Distribution of 67 Patients With LMCAD Who Had Coronary Bypass Operations*

	Group 1* (N = 24)	Group 2† (N = 28)	Group 3‡ (N = 15)	Total (N = 67)
Sex				
Male	19	22	13	54
Female	5	6	2	13
Age				
Mean	60	62	59	59
Range	44-75	44-77	47-71	44-77

LMCAD = left main coronary artery disease

*Group 1 = Patients receiving no propranolol.
†Group 2 = Patients receiving propranolol until two days before the bypass operation.
‡Group 3 = Patients receiving propranolol until the time of the bypass operation.

TABLE 2.—*Duration of Symptoms and Incidence of Unstable Angina in 67 Patients With LMCAD Who Had Bypass Operations*

	Group 1*		Group 2†		Group 3‡	
	No.	Percent	No.	Percent	No.	Percent
Symptoms						
No symptoms	2	8.2	1	3.6	0	0.0
Less than 1 year	7	29.4	6	21.5	5	33.3
1 to 5 years	8	33.3	13	46.4	5	33.3
More than 5 years	6	25.0	6	21.5	3	20.0
Unknown	1	4.1	2	7.0	2	14.3
TOTAL	24		28		15	
Unstable angina	8	33.3	14	50.0	6	40.0

LMCAD = left main coronary artery disease

*Group 1 = Patients receiving no propranolol.
†Group 2 = Patients receiving propranolol until two days before the bypass operation.
‡Group 3 = Patients receiving propranolol until the time of the bypass operation.

Patients and Materials

There were 67 patients who underwent myocardial revascularization at Pacific Medical Center in San Francisco between January 1975 and December 1978 who had documented left main coronary artery disease (LMCAD) on preoperative angiography. Of these, 44 had additional stenosis or occlusion of the right coronary artery. Patients with left ventricular aneurysm or associated valve disease were excluded from the study. Retrospectively, these patients were divided into three groups depending on the preoperative use of the β-blocking agent. Group 1 consisted of 24 patients who received no β-blocking agent for at least two weeks before the bypass operation; group 2 included 28 patients who received propranolol until two days before the operation, and group 3 included 15 patients who received propranolol until the morning of the operation.

The mean age of the patients was 59 years (range 44 to 77 years) and Table 1 gives the age and sex distribution. There was no statistical difference among the three groups for age and sex. In all three groups the majority of patients were men in the sixth and seventh decades of life.

The clinical presentation was similar for all

patients (Table 2). Two patients with no symptoms were found in group 1 and one patient in group 2 was asymptomatic. These had been selected for angiography because of abnormal results of a treadmill test. Approximately a third to a fourth of the patients had had symptoms for less than a year, a third had had symptoms for one to five years and a fourth to a fifth had had them for more than five years. Unstable angina was present in 8 patients in group 1 (33 percent), 14 patients in group 2 (50 percent) and 6 patients (40 percent) in group 3. Intra-aortic balloon counter pulsation before induction of anesthesia because of preinfarction angina was used in one patient and attempted in another in group 1, in one patient in group 2 and in two patients in group 3. Mechanical assistance was required as well in one patient in group 2 during the bypass operation. Preoperative cardiac performance was similar for all patients in each group. The ejection differences. Mean values and the range of variafraction (EF) was somewhat lower among patients in group 1, but there were no statistical tion for ejection fraction and cardiac index are listed in Table 3.

TABLE 3.—*Cardiac Index and Ejection Fraction Determinations for 67 Patients With LMCAD Who Had Coronary Bypass Operations*

	Group 1* (N = 24)	Group 2† (N = 28)	Group 3‡ (N = 15)
Cardiac index (%)			
Mean	2.70	2.40	2.55
Range	1.60-4.10	1.50-3.80	1.40-3.60
Ejection fraction (%)			
Mean	0.58	0.67	0.65
Range	0.41-0.80	0.38-0.87	0.43-0.81

LMCAD = left main coronary artery disease

*Group 1 = Patients receiving no propranolol.

†Group 2 = Patients receiving propranolol until two days before the bypass operation.

‡Group 3 = Patients receiving propranolol until the time of the bypass operation.

TABLE 4.—*Total Bypass Time, Aortic Cross Clamp Time and Number of Vessels Grafted in 67 Patients With LMCAD*

	Group 1* (N = 24)	Group 2† (N = 28)	Group 3‡ (N = 15)
Total bypass time (hr:min)			
Mean	2:42	2:30	2:24
Range	1:23-4:11	1:21-5:03	1:35-4:54
Aortic cross clamp time (min)			
Mean	61	53	60
Range	43-128	36-120	40-107
Number of vessels			
Mean	2.5	2.3	2.6
Range	2.0-5.0	2.0-4.0	2.0-3.0

LMCAD = left main coronary artery disease

*Group 1 = Patients receiving no propranolol.

†Group 2 = Patients receiving propranolol until two days before the bypass operation.

‡Group 3 = Patients receiving propranolol until the time of the bypass operation.

Intraoperative data such as total bypass time, aortic cross clamp time and number of vessels grafted are given in Table 4. Here, too, results for all three groups are very similar and without statistical differences.

Myocardial ischemic injury was evaluated by means of 12-lead electrocardiograms (EKG) taken immediately after the operation and on the morning of the first, second and third postoperative days and by measurement of serial enzyme levels. The diagnosis of definite perioperative infarction was made according to the following criteria. Definite myocardial infarction was believed to be present when new Q waves were noted in the postoperative EKG or when there was an elevation of the myocardial fraction of serum creatine phosphokinase (CPK) in combination with EKG changes. Possible myocardial infarction or subendocardial ischemia was determined by the presence of pronounced ST-T wave changes on EKG with moderate to substantial elevation of CPK-MB (CPK myocardial band) fractions. The qualitative data recorded in this communication were analyzed by the chi square test and the Student's *t* test was applied for nonpaired quantitative data.

Results

The three groups were homogeneous for age, sex ratio (Table 1), presentation and duration of symptoms (Table 2), cardiac performance (Table 3) and pertinent intraoperative data (Table 4). No major changes in the cardiopulmonary bypass protocol were made during the course of the study. There were also no significant alterations in induction or maintenance of anesthesia. All patients were operated on by using cold hyperkalemic cardiac arrest. The need for preinduction intra-aortic balloon counter pulsation was evenly distributed among the groups. The hospital mortality of the entire series was two patients (2.9 percent), one in group 1 and the other in group 2. Perioperative myocardial ischemic injury was noted in 19 patients (28 percent). Definite myocardial infarctions, however, were found in 17 percent while subendocardial ischemia was found in 11 percent (7 patients) (Table 5). There were significant differences in the incidence of both

myocardial infarction ($P<0.05$) and subendocardial ischemia ($P<0.05$) in group 2 versus groups 1 and 3. The curves for total CPK activity in serum levels during the first three postoperative days were similar, representing diffuse muscle ischemia due to hypoperfusion during extracorporeal circulation. There was, however, a statistically significant difference between the levels of CPK-MB cardiac fraction in group 2 versus groups 1 and 3 ($P<0.01$). No difference was found between groups 1 and 2 (Figure 1).

Discussion

Obstruction of the left main coronary artery carries a grave prognosis for medical therapy alone.[1-3,11] Early surgical reports suggested that the operative mortality with this lesion is also substantially increased, but with improved techniques and careful intraoperative myocardial protection the early hospital mortality is only slightly higher than in patients with more distal lesions.[1,2] Retrospective analysis of our series confirms this to be true. While distal lesions carried a risk of approximately 1 percent we found a risk of 2.9 percent for this special subgroup with LMCAD. The incidence of unstable angina among 141 patients with LMCAD was reported to be 34 percent by Cohen and co-workers.[12] A similar incidence was found in a series presented by Rajai and associates,[10] in which 40 percent were considered to have unstable angina.

The number of patients admitted to hospital for coronary artery operations who receive β-receptor blocking agents has steadily increased at our institution and most others during the last five years. Early experience in preoperative administration of propranolol had suggested a prolonged cardiac-depressing effect which might have compromised cardiac function during extracorporeal bypass. More recently, however, several reports have described severe complications after sudden discontinuation of the therapy[5,13] and even aggravation of symptoms after gradual discontinuation. Because of these conflicting reports reevaluation of the preoperative management of β-receptor blocking agents seemed to be warranted.[13,14]

The higher incidence of both definite myocardial infarctions and subendocardial necrosis in those patients in whom the β-receptor blocking treatment was discontinued during the immediate preoperative period suggests that propranolol, when part of the medical regimen, should be continued until the moment of the operation, rather

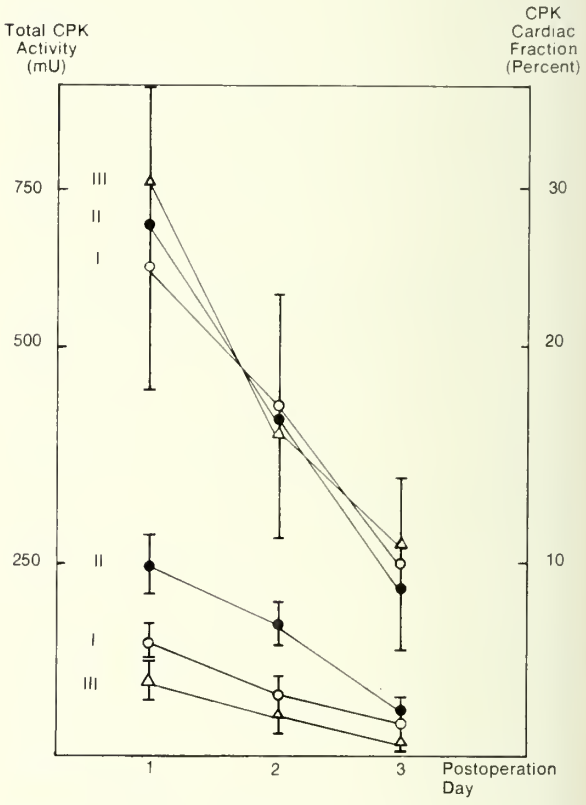


Figure 1.—Enzyme activity for total creatine phosphokinase (CPK) (mU) and cardiac fraction (percent). (I, II and III represent the three groups in the study.)

TABLE 5.—*Preoperative Myocardial Damage in 67 Patients With LMCAD*

	*Group 1**		*Group 2†*		*Group 3‡*	
	No.	*Percent*	*No.*	*Percent*	*No.*	*Percent*
No damage	19	79.0	17	60.0	12	80.0
Possible myocardial infarction (subendocardial ischemia)	2	8.3	4	14.2	1	6.6
Myocardial infarction	3	12.5	7	25.0	2	13.2
TOTAL	24		28		15	

LMCAD = left main coronary artery disease

*Group 1 = Patients receiving no propranolol.
†Group 2 = Patients receiving propranolol until two days before the bypass operation.
‡Group 3 = Patients receiving propranolol until the time of the bypass operation.

The amount of iron available from foods has decreased with the increased use of refined foods and with the lower caloric intake that accompanies a more sedentary life-style. Iron deficiency represents a problem that can be alleviated by combining food fortification programs with appropriate medical care.

REFERENCES

1. Garby L, Irnell L, Werner I: Iron deficiency in women of fertile age in a Swedish community—III. Estimation of prevalence based on a response to iron supplementation. Acta Med Scand 185:113-117, Jan-Feb 1969

2. Dallman PR, Beutler E, Finch CA: Effects of iron deficiency exclusive of anemia. Br J Haematol 40:179-184, Oct 1978

3. Bothwell TH, Charlton RW, Cook JD, et al: Iron Metabolism in Man. Oxford, Blackwell Scientific Publications, 1979, p 576

4. World Health Organization Technical Report Series No. 580: Control of Nutrition Anaemia with Special Reference to Iron Deficiency. Report of an IAEA, USAID, WHO Joint Meeting, Geneva 1975

5. Dallman PR, Siimes MA, Stekel A: Iron deficiency in infancy and childhood. Am J Clin Nutr 86-118, Jan 1980

6. Hallberg L, Hogdahl A, Nilsson L, et al: Menstrual blood loss—A population study. Acta Obstet Gynecol Scand 45:320-351, Feb 10, 1966

7. Hefnawi F, Askalani H, Zaki K: Menstrual blood loss with copper intrauterine devices. Contraception 9:133-139, Feb 1974

8. Finch CA, Cook JD, Labbe RF, et al: Effect of blood donation on iron stores as evaluated by serum ferritin. Blood 50:441-447, Sep 1977

9. Pierson RN Jr, Holt PR, Watson RM, et al: Aspirin and gastrointestinal bleeding—Chromate^{51} blood loss studies. Am J Med 31:259-265, Aug 1961

10. Committee on Nutrition, American Academy of Pediatrics: Iron supplementation for infants. Pediatrics 58:765-768, Nov 1976

11. Dallman PR, Siimes MA: Percentile curves for hemoglobin and red cell volume in infancy and childhood. J Pediatr 94:26-31, Jan 1979

12. Hemoglobin and selected iron-related findings of persons 1-74 years of age; United States, 1971-74. National Center for Health Statistics, Advance Data from Vital and Health Statistics. No. 46, pp 1-12, Jan 26, 1979

13. Svandberg B, Arvidsson B, Norrby A, et al: Absorption of supplemental iron during pregnancy—A longitudinal study with repeated bone marrow studies and absorption measurements. Acta Obstet Gynecol Scand Suppl 48:87-108, 1976

14. Okuno T: Red cell size and age. Br Med J 1:569-570, Feb 26, 1972

15. Conrad ME, Crosby WH: The natural history of iron deficiency induced by phlebotomy. Blood 20:173-185, Aug 1962

16. Piomelli S, Brickman A, Carlos E: Rapid diagnosis of iron deficiency by measurement of free erythrocyte porphyrins and a hemoglobin: The FEP/hemoglobin ratio. Pediatrics 57:136-141, Jan 1976

17. Lipschitz DA, Cook JD, Finch CA: A clinical evaluation of serum ferritin as an index of iron stores. N Engl J Med 290: 1213-1216, May 30, 1974

18. Koerper MA, Stempel DA, Dallman PR: Anemia in patients with juvenile rheumatoid arthritis. J Pediatr 92:930-933, Jun 1978

19. Eschbach JW, Cook JD: Quantitating iron balance in hemodialysis patients. Trans Am Soc Artif Intern Organs 23:54-58, Apr 21-23, 1977

20. Cook JD, Lipschitz DA, Miles LEM, et al: Serum ferritin as a measure of iron stores in normal subjects. Am J Clin Nutr 27:681-687, Jul 1974

21. Hamilton LD, Gubler CJ, Cartwright GE, et al: Diurnal variation in the plasma iron level of man. Proc Soc Exptl Biol Med 75:65-68, Jul 21, 1950

22. Stockman JA, Werner LS, Simon GE, et al: The measurement of free erythrocyte protoporphyrin (FEP) as a simple means of distinguishing iron deficiency from beta-thalassemia trait in subjects with microcytosis. J Lab Cln Med 85:113-119, Jan 1975

23. Monsen ER, Hallberg L, Layrisse M, et al: Estimation of available dietary iron. Am J Clin Nutr 31:134-141, Jan 1978

24. Cook JD, Monsen ER: Food iron absorption in human subjects—III. Comparison of the effect of animal proteins on nonheme iron absorption. Am J Clin Nutr 29:859-867, Aug 1976

25. Norrby A: Iron absorption studies in iron deficiency. Scand J Haemat Suppl 20:1-125, 1974

26. Massa E, MacLean WC Jr, Lopez de Romaña G, et al: Oral iron absorption in infantile protein-energy malnutrition. J Pediatr 93:1045-1049, Dec 1978

27. Pearson HA, Robinson JE: The role of iron in host resistance. Adv Pediatr 23:1-33, 1976

Specialty Conference

Refer to: Bashore RA, Ketchum JS, Staisch KJ, et al: Heroin addiction and pregnancy—Interdepartmental Clinical Conference, UCLA School of Medicine (Specialty Conference). West J Med 134:506-514, Jun 1981

Moderator
RICHARD A. BASHORE, MD

Discussants
JAMES S. KETCHUM, MD
KLAUS J. STAISCH, MD
CYNTHIA T. BARRETT, MD
EMERY G. ZIMMERMANN, MD

An edited transcription of an Interdepartmental Conference arranged by the Department of Medicine, UCLA School of Medicine, Los Angeles.

Heroin Addiction and Pregnancy

Pregnant heroin addicts tend to be younger than nonaddicted pregnant patients, unmarried or separated from spouses, and a disproportionately large number are members of minority ethnic groups. Heroin addiction during pregnancy is associated with several significant medical and obstetrical complications and may result in both acute and chronic abnormalities in neonates. Malnutrition, venereal disease, hepatitis, pulmonary complications, preeclampsia and third-trimester bleeding are the most common maternal complications, while fetal death, intrauterine growth retardation, prematurity and withdrawal symptoms affect the fetus and neonate. There is controversy about treating addicts with methadone during pregnancy. The findings of studies in animals suggest that there may be a long-lasting drug-induced syndrome, characterized by growth retardation, delayed motor development and behavior abnormalities in offspring of heroin-addicted or methadone-treated mothers.

RICHARD A. BASHORE, MD:* Historically, the emphasis in obstetrics has been on improving maternal welfare. With the development of antenatal care, hospital-based labor and delivery, improved anesthetic techniques, the ready availability of blood products, and the training of many professionals in obstetrics, maternal mortality and morbidity have been substantially reduced.

Perinatal loss, however, continues to be a problem and, consequently, efforts to improve fetal outcome have increased. Tests for assessing fetal well-being are now available, fetal monitoring is possible during the course of labor, and techniques for detecting fetal chromosomal abnormalities have been developed. Also, professional and technical resources in neonatal intensive care facilities are more readily available, resulting in improved care for newborns.

There is a direct correlation between factors that jeopardize maternal health and poor fetal outcome, maternal drug abuse being one specific example. This symposium focuses on heroin ad-

*Department of Obstetrics and Gynecology, UCLA School of Medicine.

Requests for reprints to: Richard A. Bashore, MD, Department of Obstetrics and Gynecology, UCLA School of Medicine, Los Angeles, CA 90024.

diction during pregnancy. Our discussants will present psychiatric and epidemiologic implications, maternal complications, the fetal and neonatal consequences and results of animal experiments that may give insight into the problem of heroin addiction in humans.

Heroin Addiction and Pregnancy: Psychiatric Implications

JAMES S. KETCHUM, MD:* Narcotic addiction during pregnancy has become an important medical condition from which we are gaining insights into human pharmacology, pathophysiology and sociology. During the past decade a national epidemic of heroin addiction occurred which, although now in recession, has left us with the problem of caring for an estimated 100,000 heroin-dependent women of childbearing age and their heroin-dependent babies. It is estimated that about 10,000 such babies are born every year. Several large hospital centers have reported significant increases in the birth of addicted babies. At the Vancouver General Hospital in Washington state, for example, offspring of heroin addicts constituted about 1 in 250 live births in 1972, a sixfold increase in 20 years.[1] At the New York Medical College Metropolitan Hospital, an increase from 1 in 164 deliveries in 1960 to 1 in 27 in 1972 was recorded.[2] The latter hospital's tenfold higher overall rate reflects its proximity to the Harlem district of Manhattan, believed to have the highest concentration of heroin addicts in the United States.

Addicted mothers and their infants have many medical problems before, during and after delivery. Most of these problems, however, are not related directly to pharmacological factors. Heroin is a potent opiate, and, unlike many drugs of abuse, opiates can be administered at high levels for long periods without serious consequences and little or no impairment of intellectual and physiological function. A heroin addict is capable of developing a high level of tolerance with repeated administration of the drug ad lib, provided there is an unlimited supply. Wikler[3] found that a detoxified morphine addict, when allowed to inject himself without restriction, increased his daily consumption from 30 mg to 1,200 mg during four months.

The appearance of pathological symptoms in an addict is related to fluctuations in narcotic levels that result in abrupt alterations in the steady state of the user. Such fluctuations were virtually unavoidable before the advent of long-acting agonists, such as methadone and, more recently, L-acetyl-alpha-methadol (LAAM, or long-acting methadone), which are administered under controlled conditions. The average addict, therefore, depending on the availability and purity of his or her drug, experiences extreme emotional instability. For these persons to maintain even partial equilibrium requires a diversion of energy from normal pursuits, and personal care, nutrition, work and human relations are therefore neglected. Desperation breaks down social conformity and this leads to criminality, self-reproach and depression.

Despite the sharp increase in the number of heroin addicts, the daily consumption per street addict has declined from an average of about 200 mg in 1950 to around 25 mg in 1974. Because the frequency and severity of the withdrawal symptoms in newborns from both of these eras are similar, it is believed that chronicity of use contributes more than daily dosage to the onset of symptoms. This is also true for methadone users.

Demographically, the pregnant addicts in most series were young (median age about 22), unmarried or separated, lacking in social supports and disproportionately concentrated in minority ethnic groups. We do not know with certainty the percentage of addicted women who become pregnant, but two opposing phenomena may have an influence: sexual drive, although suppressed under conditions of chronic use, and the costly habit, which drives as many as 50 percent of women addicts into prostitution. In the Vancouver, Washington series, parity was close to that of the general population, possibly reflecting effects of lower age, higher base rates and a short history of addiction (median of two years in one large series) in this socioeconomic category.

The cause of addiction is still unknown, although it is clearly a learned behavior requiring the acquisition of responses that result in the procurement and self-administration of the drug. These responses are presumably reinforced by both direct and indirect classic and operant mechanisms.[4] Although certain subpopulations are especially at risk, it seems that socioenvironmental circumstances are more important than constitutional or genetic influences, as witnessed by the high prevalence of addiction within the medical and pharmaceutical professions, and historically

*Department of Psychiatry, UCLA School of Medicine.

among middle-class and upper-class women. Instability of personality or psychiatric illness may increase the likelihood of drug abuse because impulsiveness and dysphoria may intensify the tendency to seek immediate gratification and relief from suffering. Alienation from societal norms, either as a result of social immaturity or mental disorder, makes antisocial behavior, including illicit drug use, more probable. Successful rehabilitation, therefore, entails more than the alleviation of tolerance and physical dependence.

The treatment of heroin addiction remains somewhat controversial. Since the introduction of methadone maintenance programs, polarization has developed within the medical community and is clearly reflected in the comments of various authors who have studied pregnant addicts and their offspring.[1,2,5] These investigators express concern about the wisdom of treating prospective mothers with methadone, citing a higher occurrence of complications and greater severity of withdrawal symptoms in the newborns. Favorable judgments, however, have been rendered by others[6-9] who found little or no neonatal mortality in a sizable series of methadone-maintained pregnant addicts. My own conclusion, after reading these reports, is that methadone is relatively safe and clearly less hazardous than heroin purchased on the street.

In the baby of a methadone-treated mother, withdrawal symptoms are qualitatively similar to those of heroin, although more delayed and persistent. Newborns presenting with these symptoms should be treated with gradually tapering doses of narcotic agonists. Although diazepam (Valium), barbiturates and phenothiazines have been described as effective in controlling neonatal abstinence, rational treatment dictates the use of opiates such as paregoric or, to obviate possible toxicity of camphor, a dilute solution of opium. When the mother has been receiving methadone under supervision, the use of methadone itself is recommended, beginning the day after delivery and gradually tapering during three to four weeks. There is no evidence that such treatment will increase the probability of later addiction. In adults, addiction should be viewed as a behavioral syndrome, requiring the learning of drug-seeking responses and the development of an awareness of, and preoccupation with, the reinforcing properties of the drug. None of these elements can be supposed to exist in a newborn infant. To refer to such infants as "addicts" and withhold all but the minimum necessary medication in their supposed interest betrays a lack of pharmacological as well as psychological insight.

As to the fate of methadone-dependent mothers, it is most encouraging to note that in the series of 120 women in a study by Newman,[6] 115 remained continuously in the treatment program after delivery. Thus, it seems that enrollment in a methadone program during or before pregnancy may prevent the high probability of reverting to the dismal life of obtaining heroin on the street after the birth of the baby. Therefore, a methadone maintenance program for the mother followed by a period of gradual methadone withdrawal for the newborn seems to be the best, if not the simplest, therapeutic strategy.

Maternal Consequences of Heroin Addiction

KLAUS J. STAISCH, MD:* Regular prenatal care is the key to prevention of complications during pregnancy, but 75 percent of pregnant heroin addicts give birth without prenatal care. However, most women enrolled in methadone maintenance programs tend to participate in regular prenatal care.[10,11] Although methadone reduces the maternal complications resulting from heroin, it has the same fetal side effects as heroin. Both drugs cause adverse effects, mainly intrauterine growth retardation and neonatal withdrawal after birth. The experience of most specialists in drug addiction suggests that a pregnant drug user is unlikely to continue in a standard prenatal program unless it is specifically adapted to her needs as an addict. The typical addict presents with medical, obstetrical and social problems. Because of the complex interrelation of these problems, pregnant women who are drug dependent need the special care of a health team consisting of an obstetrician, pediatrician and social worker, if treatment is to be successful.

It was previously thought that addicts had a reduced reproductive capacity. Findings of studies done in New York have shown that the average age of the pregnant addict is 23 years, with a mean parity of three. This indicates that women using narcotics have the same capability of becoming pregnant as those who are not addicted. The rate of spontaneous abortions and the frequency of women who seek elective abortions are the same in addicts as in the general population.[12]

The incidence of stillbirths in addicts has been

*Department of Obstetrics and Gynecology, UCLA School of Medicine.

reported to be between 17 and 60 per 1,000 births[13]; the rate in the general population is 14 per 1,000 births. Reports of stillbirths in women undergoing abrupt complete cessation of heroin use (cold turkey detoxification) are alarmingly high. During withdrawal, women report an increase in fetal movements often followed by the cessation of quickening. Serial measurements have shown that catecholamines in the amniotic fluid increase steadily during withdrawal. These changes are thought to reflect increased psychomotor activity of the fetus during the state of withdrawal. Zuspan and associates[14] have postulated that fetal death occurs during intrauterine withdrawal as a consequence of increased motor activity, leading to a relative oxygen deficit in the hyperactive fetus. Many investigators, therefore, do not recommend detoxification during pregnancy. Instead, the pregnant heroin addict should be switched to a methadone dose sufficient to prevent withdrawal. This usually requires admittance to hospital as the dose is tapered to the minimal effective maintenance dosage.

Meconium staining of the amniotic fluid, a possible sign of hypoxia, is seen three times more frequently with drug abuse and may indicate episodes of hypoxia preceding or during labor. Pregnancy in an addict can be complicated by numerous infections and other disease processes that can affect almost any area of the body. Fetal demands for growth and nourishment put further stress on an already physically debilitated addict. Because of the crisis intervention type of therapy that addicts seek and receive, it is difficult to know the true incidence of maternal and fetal morbidity.[10,15]

Malnutrition is common among heroin addicts because maintaining the drug habit usually requires that money be used for purchasing drugs and not food. In pregnant addicts, malnutrition usually causes anemia (in about 60 percent of patients), premature labor and intrauterine growth retardation. Inadequate maternal weight gain results in infants of low birth weight and high perinatal mortality. Women who register in methadone maintenance programs tend to have a more balanced diet than heroin addicts.

Many young women support their addiction by prostitution and, therefore, venereal disease occurs commonly. A positive serologic test for syphilis occurs in about 27 percent of patients. Hepatitis, usually in its chronic form, which results from the use of unclean or communal needles, is found in approximately 80 percent of the addicts. Acute hepatitis during pregnancy can cause abortion during the first and second trimesters and premature labor in the third. Although hepatitis antigen is often found in the umbilical cord blood at birth, the clinical symptoms of hepatitis are rarely seen in the neonates.[16]

X-ray studies of the chest show abnormalities in almost 90 percent of all drug addicts. Common findings include hilar lymphadenopathy and foreign body granuloma, the latter being caused by the injection of contaminated drugs. Talc, cornstarch and cotton fibers are frequently found at autopsy. Pulmonary edema and aspiration pneumonia are usually a result of drug overdose. Septic emboli from peripheral thrombophlebitis can cause pulmonary abscesses. Pulmonary fibrosis and pulmonary hypertension are examples of long-range complications of continued drug use. Bacterial endocarditis is usually related to peripheral phlebitis. The use of heroin may result in nonspecific glomerulosclerosis, a direct toxic effect of the drug on the kidneys. This condition requires symptomatic treatment and careful observation to detect superimposed preeclampsia. Skin abscesses may occur. Attempts at injecting drugs through a fibrotic vein can lead to leakage of the drug into subcutaneous tissue. Quinine, a drug used to cut heroin, causes necrosis, which in turn can be the focus of infection. Therefore, chain reactions of cellulitis, lymphangitis and lymphadenitis are commonly seen. Tetanus is an uncommon infection, but when present it carries a high mortality. In New York 75 percent of all reported cases of tetanus were related to addicts.[17] Therefore, a tetanus booster immunization in drug-dependent patients is strongly indicated.

Neonatal mortality in addicts is four times higher than in the general population. The principal causes for infant death are prematurity and growth retardation. Both of these conditions tend to occur together in the same infant and are responsible for a third of the low birth weights in addicts. The mean birth weight of heroin-addicted babies, as well as of methadone-addicted infants, is about 2,700 grams, which is considerably lower than the 3,400 grams normal birth weight in the general population. Also, breech and other abnormal presentations are seen more frequently. These conditions predispose infants to birth trauma with vaginal delivery and, if these are to be avoided, a high rate of cesarean sections.

Respiratory distress is rare in premature infants

exposed to heroin but not in those exposed to methadone.[18] The physiological basis for this finding is unclear but is thought to be due to a maturational effect of heroin on pulmonary surfactant production. Estriol values, a measure of fetoplacental function, are chronically low in methadone users and are of limited value in monitoring these high-risk pregnancies.[19] Electronic fetal monitoring of the heart rate during the antepartum period to detect fetal hypoxia is also of limited value in drug users. The cardiovascular reflexes such as beat-to-beat variability of the baseline heart rate and heart rate accelerations in response to fetal movements are signs of fetal well-being. These reflexes are blunted because of the sedative effect of methadone and heroin. Congenital abnormalities are not increased in the opiate-addicted patients.[12]

There are many problems that drug-addicted patients can present with during labor and delivery. Investigators in major cities such as New York, Philadelphia and San Francisco have reported that obstetrical complications occur in about 17 percent to 33 percent of patients. In general, complications are managed in a similar manner as with nonaddicted patients; however, physicians must be aware of the high frequency of these problems. Premature rupture of the membrane is twice as common in addicts and can lead to intrauterine infection and neonatal sepsis. Presence of infection is particularly devastating to small infants. Preeclampsia is three times as high and hemorrhage from placenta previa and abruptio placentae is four times higher in the addicted population. Management of the discomfort of labor pains presents a special problem because of addicts' developed tolerance to narcotics. High doses of analgesics would be required to control pain but these can produce neonatal depression—therefore, their use should be avoided. Epidural block is the analgesic of choice. Paracervical blocks should be given only if the estimated fetal weight is greater than 2,500 grams because it can cause fetal bradycardia, which can present a major complication to the small infant as metabolism and excretion of anesthetic drugs is slow.

When a pregnant woman uses addictive drugs, the clinical situation can become extremely complicated. To deliver effective care, physicians must be aware of the numerous medical and obstetrical problems that can arise in these women and their unborn babies. Although many hospital centers that care for obstetrical patients at high risk are working to define these problems, and indeed some of the effects of prenatal stress resulting from addiction are reversible, much remains to be done in the treatment for addicted mothers and their infants.

Fetal and Neonatal Effects of Heroin Addiction

CYNTHIA T. BARRETT, MD:* Many areas of growth, metabolism and behavior are affected in the developing fetus and newly born infant of drug-dependent mothers. The effects of heroin and methadone differ in these variables. This is thought to be true partly because of the differing direct effects of these agents and partly because of the differences in nutrition, antenatal care and general life-styles among women addicted to these two agents. In both heroin and methadone addicts there is a noticeable prevalence of abuse of other agents, including tobacco, alcohol and barbiturates, all of which have notable effects on the fetus and newly born infant.

Intrauterine growth retardation and prematurity are well-recognized complications in infants of narcotic-addicted mothers. These conditions have generally been attributed to poor nutrition of the mother, but Naeye, Blanc and Leblanc[20] and coinvestigators[21] have evidence from autopsy specimens that heroin has a primary effect on antenatal growth. In addition, they found a very high prevalence of intrauterine infection, which accounted for poor growth as well as prematurity. In infants of methadone-addicted mothers, intrauterine growth retardation occurs less frequently. There are reports, however, of diminished linear growth and head circumference during the first year of life as well as slightly decreased birth weight.[2] In 1971 Glass, Rajegowda and Evans[18] reported that respiratory distress syndrome did not occur in 33 infants prematurely delivered of heroin-addicted women. However, in 1972 Taeusch and associates[22] studied lung development in fetal rabbits and confirmed that heroin had a direct inhibitory effect on fetal growth unrelated to maternal nutrition, with some indices compatible with acceleration of lung maturation. At the time of delivery, most infants with antenatal exposure to either heroin or methadone are

*Department of Pediatrics, UCLA School of Medicine.

vigorous and have good Apgar scores. Respiratory depression may occur but it can be reversed by treatment with naloxone (Narcan).

After delivery, withdrawal symptoms are present in about 75 percent of infants of heroin addicts and in almost all infants of methadone-addicted mothers. Symptoms usually seen include hyperactivity and hyperirritability with coarse tremors and poor feeding, leading to skin abrasions and poor weight gain. Sneezing, yawning, sweating, vomiting, diarrhea and hyperthermia are present less frequently. Seizures occur in about 5 percent of infants of heroin addicts and in about 15 percent of infants of methadone addicts after therapy has been instituted. In infants of methadone addicts, one can expect more severe symptoms of withdrawal, developing later and lasting longer, than in heroin addicts. However, if the mother has been receiving a dosage of less than 20 mg per day of methadone, symptoms of withdrawal are milder and occur less frequently.

In addition to narcotic withdrawal, the differential diagnosis in an infant with symptoms of hyperactivity and hyperirritability must include hypoglycemia, hypocalcemia, hypomagnesemia and hyperthyroidism. In the presence of hyperthermia, sepsis should be ruled out, and with seizures, hyponatremia, pyridoxine dependency, meningitis and intracranial trauma must be added to the list of possible diagnoses. Even in the presence of known narcotic withdrawal, any one of the above abnormalities may be present, and laboratory studies should include all tests necessary to rule them out. In addition, examination of the urine should be done for toxic substances (often findings are negative) and of the serum for hepatitis-associated antigen (serial determinations during the first three to four months) and for serologic findings (there is an increased prevalence of syphilis in heroin addicts).

Recognizing the withdrawal state of an infant is critical because most deaths are due to dehydration, which occurs when the baby is discharged from a hospital nursery in undiagnosed narcotic withdrawal. With proper diagnosis and use of current techniques in caring for these high-risk infants, neonatal mortality need not reach 5 percent, with the major causes of death being prematurity, infection and perinatal asphyxia, and not withdrawal.

The care of an infant during withdrawal involves supportive measures aimed at decreasing physical stimuli to the baby and providing as calm an environment as possible in the high-risk nursery setting. Often by holding and rocking a baby and giving it a pacifier, one can alleviate much of the hyperactivity and hyperirritability that occurs during withdrawal, thereby eliminating the need for pharmacological intervention. Normal fluid balance can be maintained by use of gavage feeding. In the presence of notable vomiting or diarrhea, however, it may be necessary to give fluids intravenously.

The pharmacological agents used in the management of the withdrawal state include sedatives and narcotic substitutes. Various regimens using both groups of drugs have proved effective. The sedatives most frequently used are diazepam, phenothiazine and phenobarbital. Diazepam usually requires the shortest duration of therapy, often less than a week, but it does not reduce diarrhea. This agent is not recommended for patients with jaundice because the sodium benzoate in the diluent will displace bilirubin from albumin and increase the risk of bilirubin encephalopathy. Phenothiazine and phenobarbital often require courses of therapy as long as three weeks for complete withdrawal. There is a noticeable prevalence of extrapyramidal signs associated with phenothiazine that may occasionally be confused with signs of withdrawal.

Phenobarbital, in doses required to provide symptomatic relief, may produce lethargy and augment the nutritional problem. Also, it is ineffective against diarrhea. Phenobarbital may be used in babies with jaundice because it induces activity of glucuronyl transferase and may thus reduce the severity and duration of neonatal jaundice. It does not displace bilirubin from albumin. Diazepam and phenobarbital should never be used together in management of newly born infants because of increased risk of respiratory arrest. Jaundice is a less prevalent problem in infants with antenatal exposure to heroin than in the normal population because heroin is thought to induce glucuronyl transferase activity. The effects of methadone on this enzyme system are not known. Infants with glucose-6-phosphate dehydrogenase deficiency, however, may have increased severity of neonatal jaundice because quinine is frequently used to cut heroin.

Paregoric, which is a camphorated tincture of opium, is the narcotic substitute most frequently used. This agent is particularly effective in

infants with diarrhea and may even produce constipation. When paregoric is used to treat withdrawal symptoms, the most common side effect is lethargy, which tends to decrease nutrition; weaning is often prolonged to six weeks. Methadone has not been widely used to treat withdrawal symptoms, although there are some reports of its being used with success. In one study, duration of time in hospital was not different among three groups of infants treated with methadone, diazepam and phenobarbital.[24] Recently, we treated two addicted infants with breast-feeding by their mothers who were in methadone maintenance programs; no pharmacological agent was used and neither baby had any notable withdrawal symptoms.

The effects of methadone and heroin, as well as the pharmacological agents used in treating withdrawal on neonatal adaptive behavior, have been investigated: methadone depresses adaptive behavior to a greater extent than heroin. When nutritive sucking was the variable studied, infants treated with paregoric during withdrawal had nearly normal adaptive behavior; those treated with phenobarbital had less normal behavior, and those with diazepam had very abnormal adaptive behavior.

Late signs of methadone and heroin withdrawal persist in about 5 percent to 10 percent of children and are more severe after methadone withdrawal, usually lasting as long as three months. After heroin withdrawal, more than 20 percent of infants are hyperactive and have a short attention span even at 1 year of age. Infants withdrawing from methadone have an increased frequency of all behavioral disturbances up to 18 months of age. Thereafter these abnormalities seem to resolve. Increased prevalence of behavioral disturbances has not been noted in infants whose mothers received less than 20 mg of methadone per day.

Sudden infant death syndrome has been reported in about 2 percent of infants after heroin or methadone withdrawal. This is seven times higher than in the normal population. The cause is unknown, but it may be related to an increased frequency of abnormal sleep states in these infants.

Despite the more severe and prolonged withdrawal symptoms in infants receiving methadone antenatally, this agent is preferable to heroin during the antepartum period because of the many social and legal complications involved with heroin use. Whereas most infants born to heroin-addicted women are removed from the mother and placed in foster care, methadone-maintained women generally keep their babies. It is hoped that a heroin substitute will be found that will have fewer side effects than methadone in newly born infants exposed to heroin antenatally.

Research Methods in Drug Abuse

EMERY G. ZIMMERMANN, MD:* Adverse consequences of maternal narcotic addiction for the developing fetus and newborn have been noted with increasing frequency by clinicians[5] during the past 25 years.[25] The increase in opiate abuse by women of childbearing age during the past decade has brought the problem of fetal and neonatal narcotic addiction into sharp focus. The problems experienced by pregnant addicts and their addicted offspring have been discussed by previous speakers at this conference. In this section I will briefly review recent experimental animal research in the problem of neonatal narcotic addiction.

Rats are used extensively for studying developmental effects of opiates because many of their responses to drugs resemble those of humans and because of their short life span. Findings of current studies in rats confirm results obtained in clinical investigations.

Administration of opiates, whether morphine or methadone, during fetal development results in increased intrauterine death,[26-28] decreased body and brain growth[27,29-31] and characteristic neonatal narcotic withdrawal.[26-28] Additional findings include retardation of motor development and delayed behavioral maturation.[28,31-33] Narcotics are not morphologically teratogenic in rodents or in humans except at high doses.[34] The effects of narcotics on the developing organism are more subtle in that they seem to alter the rate and extent of growth and functional maturation. It is difficult to study these variables of development in humans because of the many genetic and environmental factors involved. Animal studies are particularly valuable in that they allow systematic variation of experimental conditions.

Virtually all animal studies have shown that both morphine[26,27,29,31,35-37] and methadone,[30,38] when administered during intrauterine development, result in growth retardation in the neonate. Moreover, the growth lag persists, in most cases, for weeks to months after birth. The absence of catch-up growth suggests that nutritional impairment may not fully explain the growth retardation

*Departments of Anatomy and Neurology, UCLA School of Medicine.

and that additional long-lasting drug-induced neurochemical alterations may be involved. The immature brain seems to be particularly vulnerable to actions of opiates. Opiate-specific receptors appear in the rat brain about midgestation.[39] Steele and Johannesson[29] found that morphine administered to maternal rats near term (21 days gestation) appeared in almost equal amounts in the fetal and maternal brains. Peters[38] found similar disbursement of methadone in pregnant rats and fetuses, with some delay in distribution to the fetal brain. Methadone appeared in higher concentrations in the blood of pregnant animals than in nonpregnant animals. Peters also noted that because of the lack of a blood-brain barrier in the developing organism, the concentration of methadone in the fetal brain approximated that found in the rest of the carcass. Zagon and McLaughlin[27,30] reported that morphine and methadone administered to rats during pregnancy caused decreased brain weight and size in addition to decreased litter size, increased number of stillborns, increased pup mortality and decreased neonatal birth weight. The effects on growth and weight seem to be related to the dose of opiate administered.

Behavioral effects of perinatal exposure to opiates clearly outlast the presence of the drug or its metabolites in the body. Peters[38] correlated neurochemical changes and behavioral deficiencies in offspring of rats treated with morphine or methadone throughout gestation and lactation (21 days). Offspring exposed to morphine and methadone were slow to learn to run a maze and to acquire shock avoidance behavior. We found similar behavioral effects long after neonatal administration of morphine.[33,35,36] Banerjee[32] reported impaired acquisition of conditioned avoidance responses in rats seven weeks after exposure to morphine early in life, and we observed altered conditioned emotional responses as long as three months after neonatal exposure to morphine.[33,35]

Delayed development of motor function has also been reported to follow early exposure to opiates.[28] Several spontaneous and reflex motor behaviors appeared later and developed more slowly in pups exposed to methadone during gestation and lactation. These effects seem to be related to the time and duration of drug exposure.

Other effects of early exposure to opiates have been observed in experimental studies using rodents. Several investigators have noted the development of tolerance to the analgesic action of morphine or methadone.[26,29,33] In our experiments we detected tolerance for as long as 230 days[31,35] and evidence of drug dependence for up to 90 days[37] after administration of morphine to neonates. Alterations in neuroendocrine function have also been reported.[31,33,36,37] Although the effects of perinatal opiate dependence are not clearly understood, they may help explain the persistent growth and behavioral effects of early exposure to opiates. In addition, findings of several studies have shown body-weight and motor deficits in the offspring of rats that were themselves treated with opiates early in life.[40] The significance of these carry-over effects into subsequent generations remains to be elucidated.

The mechanism by which perinatal opiate exposure exerts long-lasting effects on growth and development is not known with certainty but seems to involve altered neurochemical development. Steele and Johannesson[41] were among the first to show that growth retardation is associated with decreased macromolecular synthesis in the brain. This suggests that prenatal administration of morphine causes a dose-dependent interference with cerebral protein synthesis by decreasing the availability of mRNA. Several other investigators have confirmed that chronic administration of morphine or methadone to rats during the perinatal period causes significant decrease of brain protein, RNA and DNA in the offspring.[38,41,42] Further studies with rats should clarify the biochemical basis of the aforementioned effects of perinatal opiate addiction.

In summary, the advantages of methadone maintenance during pregnancy and the successful management of addicted newborns are noteworthy achievements. However, the long-term consequences for developing infants remain obscure. Such effects have recently begun to attract serious attention as a result of the growing awareness of an apparent long-lasting drug-induced syndrome consisting of growth retardation, delayed motor development and behavioral abnormalities. Although this syndrome is not limited to opiate use, the appearance of drug-specific features, such as tolerance and dependence, offer sufficient evidence to implicate opiates, including heroin and methadone, in the production of the generalized syndrome of drug-delayed development (3D syndrome). Results of clinical and experimental studies recently have been reviewed, and they show the urgent need for information about the long-term and perhaps permanent effects of

abused drugs on developing fetuses.[12] For reasons of economy of time and dollars, well-established studies using rats should once again prove useful in this research.

REFERENCES

1. Fricker HS, Segal S: Narcotic addiction, pregnancy and the newborn. Am J Dis Child 132:360-366, Apr 1978

2. Zelson C, JaLee S, Casalino M: Neonatal narcotic addiction—Comparative effects of maternal intake of heroin and methadone. N Engl J Med 289:1216-1220, Dec 6, 1973

3. Wikler A: Opiate Addiction; Psychological and Neurophysiological Aspects in Relation to Clinical Problems. Springfield, IL, Charles C Thomas, 1953

4. Wikler A: Dynamics of drug dependence—Implications of a conditioning theory for research and treatment. Arch Gen Psychiatry 28:611-616, May 1973

5. Naeye RL, Blanc W, Cheryl P: Effects of maternal nutrition on the human fetus. Pediatrics 52:494-503, Oct 1973

6. Newman RG: Pregnancies of methadone patients. NY State J Med 74:52-54, Jan 1974

7. Stimmel B, Adamsons K: Narcotic dependency in pregnancy—Methadone maintenance compared to use of street drugs. JAMA 235:1121-1124, Mar 1976

8. Blinick G, Jerez E, Wallach R: Methadone maintenance, pregnancy and progeny. JAMA 225:477-479, Jul 30, 1973

9. Blatman S. Methadone and children. Pediatrics 48:173-175, Aug 1971

10. Connaughton JF, Reeser D, Schut J, et al: Perinatal addiction—Outcome and management. Am J Obstet Gynecol 129:679-686, Nov 1977

11. Finnegan L, Reeser D, Connaughton J: The effects of maternal drug dependence on neonatal mortality. Drug Alcohol Depend 2:131-140, Mar 1977

12. Rementeria JL (Ed): Drug Abuse in Pregnancy and Neonatal Effects. St. Louis, CV Mosby Company, 1977, p 4

13. Rementeria JL, Nuany NN: Narcotic withdrawal in pregnancy—Stillbirth incidence with a case report. Am J Obstet Gynecol 116:1152-1156, Aug 15, 1973

14. Zuspan FP, Gumpel JA, Mejia-Zelaya A, et al: Fetal stress from methadone withdrawal. Am J Obstet Gynecol 122:43-46, May 1, 1975

15. Perlmutter JF: Maternal morbidity in the pregnant drug addict, chap 3, *In* Rementeria JL (Ed): Drug Abuse in Pregnancy and Neonatal Effects. St. Louis, CV Mosby Company, 1977, pp 30-39.

16. Schweitzer IL, Mosley JW, Ascavai M, et al: Factors influencing neonatal infection by hepatitis B virus. Gastroenterology 65:277-283, Aug 1973

17. Brust JCM, Richter RW: Tetanus in the inner city. NY State J Med 74:1735-1742, Sep 1974

18. Glass L, Rajegowda BK, Evans HE: Absence of respiratory distress syndrome in premature infants of heroin-addicted mothers. Lancet 2:685-686, Sep 25, 1971

19. Bashore RA, Westlake JR: Plasma unconjugated estriol values in high-risk pregnancy. Am J Obstet Gynecol 128:371-380, Jun 15, 1977

20. Naeye RL, Blanc WA, Leblanc W: Heroin and the fetus (Abstract). Pediatr Res 7:321, Apr 1973

21. Naeye RL, Blanc WA, Leblanc W, et al: Fetal complications of maternal heroin addiction—Abnormal growth, infections, and episodes of stress. J Pediatr 83:1055-1061, Dec 1973

22. Tacusch HW Jr, Carson S, Wang NS, et al: The effects of heroin on lung maturation and growth in fetal rabbits (Abstract). Pediatr Res 6:335, Apr 1972

23. Madden JD, Chappel JN, Zuspan F, et al: Observation and treatment of neonatal narcotic withdrawal. Am J Obstet Gynecol 127:199-201, Jan 15, 1977

24. Kron RE, Kaplan SL, Phoenix MD, et al: Behavior of infants born to drug-dependent mothers—Effects of prenatal and postnatal drugs, chap 12, *In* Rementeria JL (Ed): Drug Abuse in Pregnancy and Neonatal Effects. St. Louis, CV Moshy Company 1977, pp 129-144

25. Zelson C Rubio E, Wasserman E: Neonatal narcotic addiction—Ten-year observation. Pediatrics 48:178-189, Aug 1971

26. Johannesson T, Becker BA: The effects of maternally administered morphine on rat foetal development and resultant tolerance to the analgesic effect of morphine. Acta Pharmacol Toxicol 31:305-313, Jul 1972

27. Zagon IS, McLaughlin PJ: Effects of chronic morphine administration on pregnant rats and their offspring. Pharmacology 15:302-310, Nov 1977

28. Zagon IS, McLaughlin PJ: Perinatal methadone exposure and its influence on the behavioral ontogeny of rats. Pharmacol Biochem Behav 9:665-672, Nov 1978

29. Steele WJ, Johannesson T: Effects of prenatally administered morphine on brain development and resultant tolerance to the analgesic effect of morphine in offspring of morphine treated rats. Acta Pharmacol Toxicol 36:243-256, Mar 1975

30. Zagon IS, McLaughlin PJ: The effects of different schedules of methadone treatment on rat brain development. Exp Neurol 56:538-552, Sep 1977

31. Zimmermann E, Sonderegger T, Bromley B: Development and adult pituitary-adrenal function in female rats injected with morphine during different postnatal periods. Life Sci 20:639-646, Feb 15, 1977

32. Banerjee U: Conditioned learning in young rats born of drug-addicted parents and raised on addictive drugs. Psychopharmacologia (Berlin) 41:113-116, 1975

33. Sonderegger I, Zimmermann E: Adult behavior and adrenocortical function following neonatal morphine treatment in rats. Psychopharmacology (Berlin) 56:103-109. Jan 31, 1978

34. Iuliucci JD, Gautieri RF: Morphine-induced fetal malformations—II. Influence of histamine and diphenhydramine. J Pharm Sci 60:420-425. Mar 1971

35. Sonderegger T, Zimmermann E: Persistent effects of neonatal narcotic addiction in the rat, chap 36, *In* Ford DH, Clouet DH (Eds): Tissue Responses to Addictive Drugs. New York, Spectrum Publications, 1976, pp 589-609

36. Sonderegger T, O'Shea S, Zimmermann E: Consequences in adult female rats of neonatal morphine pellet implantation. Neurobehav Toxicol 1:161-167, 1979

37. Zimmermann E, Branch B, Taylor AN, et al: Long-lasting effects of prepubertal administration of morphine in adult rats, *In* Zimmermann E, George R (Eds): Narcotics and the Hypothalamus. New York, Raven Press, 1974, pp 183-196

38. Peters MA: Studies on the time course distribution of methadone in the pregnant, nonpregnant, male and fetal rat. Proc West Pharmacol Soc 16:70-76, 1973

39. Clendeninn N, Petraitis M, Simon EJ: Ontological development of opiate receptors in rodent brain, *In* Kosterlitz H (Ed): Opiates and Endogenous Opioid Peptides. Amsterdam, North Holland Press, 1976, pp 261-266

40. Zimmermann E, Sonderegger T, Overing S: Abnormalities in the untreated offspring of female rats treated neonatally with morphine (Abstract). Neuroscience Abstracts, Vol III, Seventh Annual Meeting of Society for Neuroscience, Anaheim, California Nov 6-10, 1977, p 305

41. Steele WJ, Johannesson T: Effects of morphine infusion in maternal rats at near-term on ribosome size distribution in foetal and maternal rat brain. Acta Pharmacol Toxicol 36:236-242, Mar 1975

42. Johannesson T, Steele WJ, Becker BA: Infusion of morphine in maternal rats at near-term—Maternal and foetal distribution and effects on analgesia, brain DNA, RNA and protein. Acta Pharmacol Toxicol 31:353-368, Nov 1972

Refer to: Cello JP: Diverticular disease of the colon—Medical Staff Conference, University of California, San Francisco. West J Med 134:515-523, Jun 1981

Diverticular Disease of the Colon

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr, Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR. SLEISENGER:* *In this Grand Rounds, Dr. John Cello will discuss the clinical spectrum of diverticular disease of the colon.*

DR. CELLO:† Preoccupation and even frank fascination with colorectal function has characterized medicine since at least the third millenium before the birth of Christ. To the ancient Egyptians, an internist was called a *Swnw* (pronounced "soo noo") or shepherd of the anus.[1] The anus was for Egyptian anatomists a second rallying point for the great vessels after the heart, receiving mucus from the nose and air from the lungs. The vessels around the anus, according to this archaic pathophysiology, could dilate and become flooded with stool that contained a dangerous element of putrefaction called *ukhedu*. This pathophysiologic tenet among other beliefs necessitated the elaborate funeral practices that ranged from low-cost postmortem purification enemas to the more elaborate bowel cleansing and storage of viscera in expensive canopic jars. This fascination with colonic function continued well into the era of modern medicine. In fact, the very name we call ourselves, physicians, was derived from the most important form of medical therapy available to medieval health practitioners, namely, *physic*, or enemas and cathartics.

A condition unknown to the ancient Egyptians, medieval health practitioners or even the anatomists of the 18th and 19th centuries, colonic diverticular disease is now one of the most prevalent disorders in Western society. I will review our understanding of the epidemiology and experimental data on diverticular disease and try to develop a theory of its pathophysiology. I will also discuss the two most important clinical consequences of colonic diverticular disease—diverticulitis and diverticular hemorrhage—and the current concept of how fiber therapy might affect outcome of the disease. However, some definitions need to be given first.

Diverticulosis of the colon is merely the presence of colonic diverticula. *Diverticulitis*, on the other hand, is the inflammatory process that develops in and around a perforated diverticulum. Because fiber is discussed whenever diverticular disease is reviewed, there are two additional definitions which need to be clarified. Crude fiber, a term widely misused on cereal box tops and even in the dietary literature, is the residue of plant cells following in vitro extraction with dilute acid and dilute alkali. Dietary fiber, on the other hand, is about four to eight times the weight of crude fiber and consists of the residue left behind after the

*Marvin H. Sleisenger, MD, Professor and Vice-Chairman, Department of Medicine; Chief of the Medical Service, Veterans Administration Medical Center, San Francisco.

†John P. Cello, MD, Assistant Professor of Medicine and Chief of the Gastrointestinal Unit, San Francisco General Hospital.

normal in vivo digestive process. Chemically, dietary fiber is the hemicellulose, cellulose and lignin products contained in foods of vegetable origin.

Epidemiology

Colonic diverticular disease is extremely uncommon in humans in underdeveloped areas. It is also distinctly uncommon in men and women everywhere before the third and fourth decades of life. However, in Western society, since the early part of this century, diverticular disease has become so prevalent that it is found in more than 50 percent of persons in the eighth or ninth decades of life on postmortem examination.[2] Epidemiologic evidence associates dietary fiber intake, colonic function and the appearance of colonic diverticular disease in human society. Why the sudden onset of colonic diverticular disease in an extraordinarily high percentage of the population since about 1920? If one examined the dietary fiber intake of persons in Great Britain, Europe and the United States until the 1880's, one would find daily *crude* fiber intakes of about 3 grams, or 12 grams of *dietary* fiber. Flour was a major constituent of their diet and consisted of about 0.5 percent dietary fiber. Following the introduction of milling of grains by steel roller, first in Great Britain and then in the rest of the Western world, the fiber content of flour dropped to about a tenth of its former level. Moreover, flour and grain consumption began to fall by the late 19th century.[3]

Within any given society, the dietary fiber intake of persons *with* colonic diverticula, is significantly lower than age-matched and socioeconomic-matched controls who do not have colonic diverticula.[4,5] In certain societies, such as in Africa and Latin America, there is substantial consumption of homegrown and homeprocessed products. Associated with this high residue, high fiber diet, is a more natural colonic function, with stool weights of 400 grams or greater (Figure 1). Stool transit time in members of these societies is 24 to 36 hours, considerably different from that of English adult students, for example, who have daily fecal weights of around 100 grams and prolonged transit times of about 72 hours.[6] The low fecal weight and prolonged transit time are fairly common in persons in Western society on low residue diets. In populations with large daily fecal weights, short transit times and high fiber consumption, colonic diverticula are virtually unknown. The introduction of radiographic techniques throughout Africa has permitted documentation of the prevalence of diverticular disease. Previously, only one in 2,000 autopsies conducted in blacks in Johannesburg, South Africa, showed evidence of colonic diverticular disease. It was likewise virtually unknown in the Indian subcontinent. However, with increasing urbaniza-

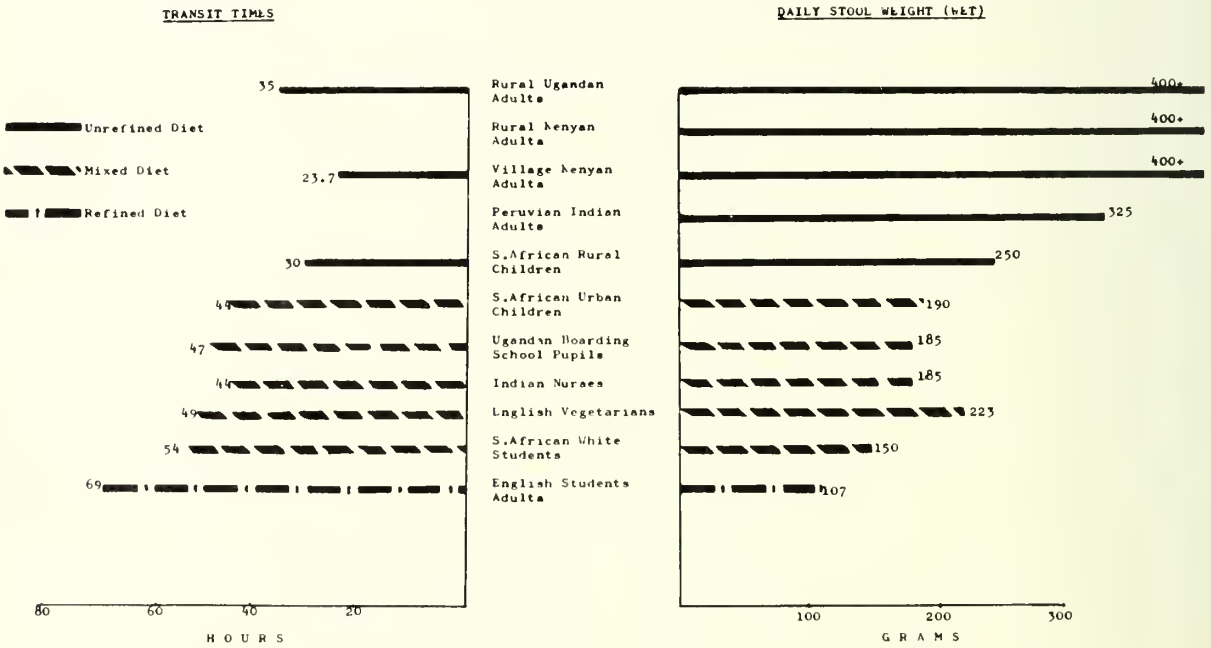


Figure 1.—Intestinal transit times and daily stool weights in different communities. (Reproduced with permission from Burkitt.[6])

tion and with the introduction of a more processed diet, urbanized African blacks now have an increased prevalence of colonic diverticular disease.[7,8]

Animal Studies

Findings of studies in animals have also related dietary fiber intake, colonic function and the development of diverticula. In rhesus monkeys subjected to decreased intake of dietary fiber while being maintained on the other constituents of their diets, distinct changes in colonic function developed.[9,10] Intraluminal pressure catheters as well as electrodes and strain gauges monitored myoelectric activity in the left colon of the animals. Similar to epidemiologic findings in humans on low residue diets, the rhesus monkeys had dramatic decreases in daily dry fecal weights. Also, in the descending colon and sigmoid colon a substantial increase in intraluminal pressures occurred, accompanied by increases in resting colonic activity (that is, nonpropulsive, nonperistaltic activity) (Figures 2 and 3). In these experimental animals colonic diverticula did not develop, probably because of the short duration of the low residue diet. However, in rabbits fed a low residue diet of white bread, milk and a vitamin and mineral supplement over four months, decreases in daily fecal weights and increases in myoelectric activity were noted.[11] Colonic diverticula, predominantly in the left colon, developed in the rabbits.

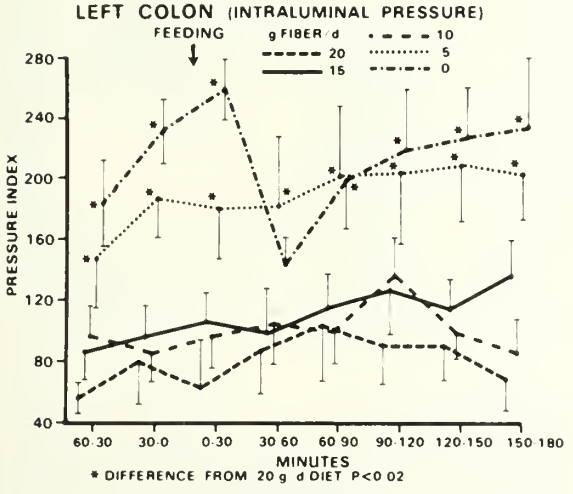


Figure 2.—Colonic intraluminal pressure index before and after modifying fiber content of diet in rhesus monkeys. Substantial changes were noted between 0 and 5 grams intake and other diets higher in fiber. (Reproduced with permission from Brodribb et al.[9])

Pathophysiology

The above epidemiologic and experimental data provide some basis for a pathophysiologic understanding of the development of colonic diverticula. Our current concept of the development of colonic diverticula associates a decrease in residue in the diet with increased intraluminal pressures. Under such increasing intraluminal pressure, predominantly in the left colon, colonic diverticula develop. These occur on the mesenteric side of the antimesenteric taenia, the site at which the perforating mesenteric arterioles course through the obliquely arranged tissue septa of the circular smooth muscle. It appears that for diverticula to develop

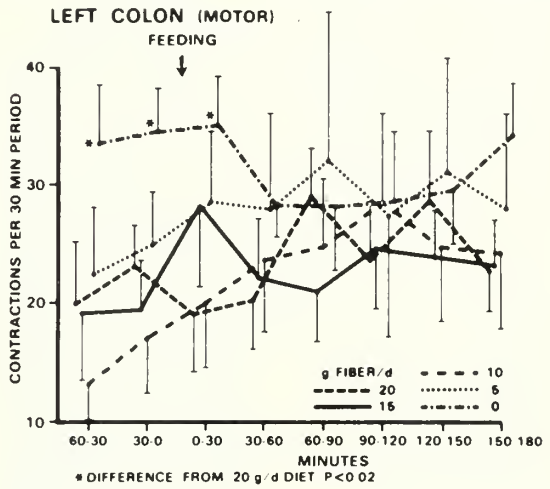


Figure 3.—Mean number of contractions of colon circular smooth muscle in monkeys before and after feeding diets of varying fiber content. (Reproduced with permission from Brodribb et al.[9])

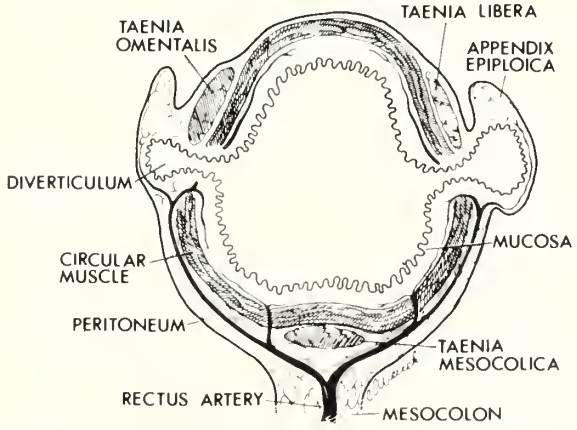


Figure 4.—Cross-section anatomy of a diverticula-bearing colon segment. The two colonic diverticula shown have herniated through the tissue septa on the mesenteric side of the antimesenteric taeniae (labelled taenia libera and taenia omentatis). (Reproduced with permission from Berman & Kirsner.[12])

in animals, the longitudinal smooth muscle must be grouped into bands or taenia (Figure 4). When seen at the time of pathological evaluation, most of the diverticula are very small, narrow-mouthed orifices projecting from virtually every segment of the left colon. They are particularly prevalent in the narrowest portion of the colon, sigmoid and descending colon. During an in vivo colonoscopic evaluation, virtually every interhaustral area in the left colon may contain many of these small-mouthed diverticula. In some cases, they can become quite large. They are very difficult to see on rigid proctosigmoidoscopy, however, because they invariably begin in the intra-abdominal portion of the left colon. In barium enema radiography in persons in their seventh, eighth and ninth decades of life, every interhaustral area on the descending colon and sigmoid colon may have one or more diverticula (Figure 5). A disproportionate number of them occur in the left colon in humans.

Figure 5.—Extensive colonic diverticulosis. Numerous small diverticula are noted throughout the colon, though the greatest number are in descending and sigmoid colon.

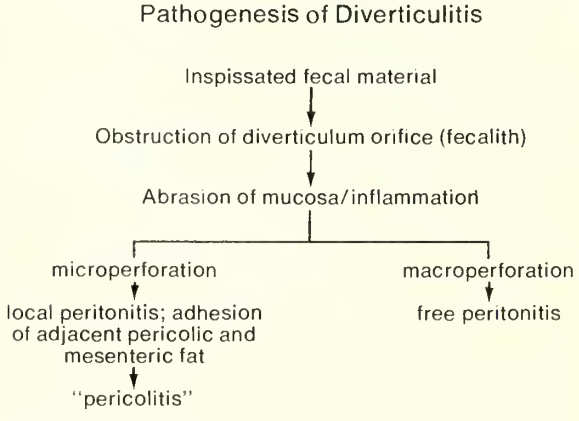


Figure 6.—Proposed pathogenesis of diverticulitis. The actual events leading to the perforation are undocumented.

Traditionally, a broad range of symptoms have been attributed to the presence of colonic diverticula, most of which are related to the low residue diet itself. Complications involving colonic diverticulosis were noted in a study conducted by the Lahey Clinic in Boston. Following a cohort of 294 asymptomatic patients who had had incidental barium enema studies that showed colonic diverticula, the investigators prospectively analyzed the complications that occurred over 15 years.[13] During this time, clinical diverticulitis developed in 25 percent, obstruction in 5 percent, clinical perforation in 5 percent and substantial hemorrhage in 5 percent of these patients.

The most common complication of colonic diverticular disease is diverticulitis. It is important to stress that diverticulitis is not primarily an infectious, inflammatory process in the *lumen* of the diverticulum. It is first and foremost a *perforation* of the diverticulum. The events that lead to such perforations, however, are unknown. The most common theory suggests that it is somehow related to the inspissation of fecal material and obstruction of the diverticulum orifice. Abrasion of the mucosa of the diverticulum then leads to perforation (Figure 6). Demonstrated by careful pathological and radiographic evaluation, the vast majority of patients with diverticulitis will be found to have a microperforation of the colon. The majority of these microperforations, fortunately, are subclinical. Due to the adjacent peritoneal inflammation, the mesentery and adjacent bowel prevent the extension of this inflammatory process outside the confines of the left colon. Thus, diverticulitis is not a diverticular infection, but a *pericolitis* in which the adjacent serosal surface of the bowel is intimately involved in the inflammatory reaction. In a small percentage of patients with diverticulitis a free perforation with gross peritonitis does develop. By radiographic barium contrast, it is possible in some patients

with diverticulitis to demonstrate the site of perforation with a small amount of barium collecting outside the lumen. More characteristically, spasm, edema and focal narrowing of the colon are noted on radiographic studies (Figures 7 and 8).

Clinically, diverticulitis is manifested by left lower quadrant abdominal pain and altered bowel habits. Most patients have constipation, but diarrhea may occur occasionally in patients with a critically narrowed but not obstructed colon. Radiographically, the differential diagnosis is extensive, including diverticular disease, carcinoma, ischemic colitis, Crohn colitis and radiation colitis. The major clinical problem, however, is differentiating between diverticular disease and a colonic malignancy. Careful radiographic and colonoscopic follow-up studies and even an operation are often required to clarify the diagnosis.

Forms of Treatment

Colonic diverticulosis, with its broad range of nonspecific symptoms, most of which are probably related to the low residue diet itself, is best treated by efforts to increase the roughage in the diet. Wheat bran, stool softeners and hydrophilic colloids are widely used, although they are of relatively undocumented efficacy in preventing the complication of diverticulitis. There is no documented evidence that any particular food products are directly responsible for obstructing the diverticulum orifice and precipitating the perforation. Anticholinergic and antispasmodic drugs, analgesic agents, sedatives, and tranquilizers widely prescribed for diverticulosis actually have little clinical research to support their use.[3] For mild diverticulitis, most patients—even though they have colonic microperforation—respond to conservative medical therapy at home on a low residue diet (if constipated). The use of orally given antibiotic drugs is of undocumented efficacy, particularly the orally given nonabsorbable antibiotic agents, because the inflammatory infectious process is extraluminal. Once again, anticholinergic and antispasmodic agents do not have any documented place in the therapy of mild diverticulitis.

For severe attacks of diverticulitis, character-

Figure 7.—Barium enema study in diverticulitis. Extensive haustral thickening from spasm and edema are noted in the sigmoid colon. No free perforation is demonstrated.

Figure 8.—Barium enema study in diverticulitis. Extraluminal contrast material is shown passing from the narrowed sigmoid colon to a small pelvic abscess. Fistula formation to bladder or vagina may follow.

ized by colonic obstruction, severe left lower quadrant abdominal pain, fever, leukocytosis and a palpable, tender sausage-shaped mass in the left lower quadrant, admission to hospital is required. Routinely, neither solid foods nor liquids should be given orally for the first few days, especially if there is a clinically apparent obstruction. Diagnostically, the initial radiographic studies should consist of only plain supine and upright films of the abdomen. Sigmoidoscopy should be gently carried out to exclude distal rectosigmoid mass obstruction. Barium enema studies are unnecessary and potentially harmful during the first several days of the hospital stay. If, however, a colon contrast study is needed during the first few days, water-soluble agents, such as Hypaque (diatrizoate sodium solution) should be used rather than barium. If barium mixed with stool contaminates the peritoneal cavity it can present a substantial and formidable problem for the surgeon and is liable to produce abscesses and adhesions. Analgesic agents such as meperidine are used routinely for pain. There are, unfortunately, few data concerning antibiotic therapy in diverticulitis.[3] Because we are dealing with a focal area of fecal contamination in the peritoneum involving some 10^{12} organisms per gram of stool, one would think that broad spectrum antibiotic therapy including anaerobic coverage would be essential. Unfortunately, this has not been documented and the broadest of clinical experience has been with ampicillin therapy alone. There is some clinical anecdotal experience with use of the aminoglycosides, such as tobramycin or gentamicin, and clindamycin in patients with severe inflammatory processes in-involving the left colon that have resulted from diverticulitis. In acutely ill septic patients such additional antibiotic therapy is justified.

There is good evidence that high fiber intake in therapeutic or pharmacological quantities provides substantial changes in colonic function.[14-17] There are no data, however, to suggest that the colonic diverticula either decrease in size, disappear, or are less prone to develop diverticulitis or diverticular hemorrhage. In some studies, there is supportive evidence that during administration of bran, prolonged transit times decrease to normal and fecal weights increase to over 200 grams per day. There is some evidence from motility studies conducted in patients receiving a high fiber diet that the elevated motility index may return to normal in the sigmoid colon.[16] Preprandial, interprandial and postprandial high-pressure colonic activities decrease with a high residue diet. Several British studies, moreover, suggest there can be substantial amelioration of symptoms in persons with colonic diverticulosis who eat a high fiber diet.[18] The problem with the data is, of course, the broad range of symptoms that are attributed to the mere presence of colonic diverticula. Also, it requires several months of therapy for a high fiber diet to produce substantial amelioration of symptoms.[18] Evidence from most of the studies on diverticular disease and its response to a high fiber diet suggests that a trial of three months of therapy is warranted.

TABLE 1.—*Fiber Therapy for Diverticular Disease**

Product	*Amount to Produce 20 Grams of Fiber*
Unprocessed bran	45 grams (1½ oz).
All-Bran/Bran Buds	68 grams (2¼ oz.)
Bran Chex	135 grams (4½ oz.)
Total (cereal)	270 grams (9 oz.)
Whole meal bread	404 grams (13½ oz.)
Whole carrots	681 grams (22½ oz.)
Cabbage	775 grams (26 oz.)
Apples (fresh)	1,477 grams (49 oz.)

*Equivalent weights of dietary products required to produce 20 grams of fiber intake and approximate doubling of daily fecal weight.

In general, most of the literature suggests that a doubling of fecal weights is necessary to produce substantial decreases in intraluminal pressures in the left colon.[19] Doubling of stool weights in humans requires a 15 to 20 gram intake of dietary fiber. In our society, the most efficacious method is through ingestion of fairly high concentrations of unprocessed wheat bran. Although this product has the palatability and consistency of redwood sawdust, eating about an ounce and a half, or 6 level tablespoons, provides about 20 grams of fiber and will substantially ameliorate many of the symptoms of colonic diverticular disease. There are commercial cereals, such as All Bran and Bran Buds, which in about 2¼ ounce portions (about two bowls) also supply about 20 grams of dietary fiber. The other cereals that are allegedly high in bran are less so, and one would have to consume half a pound of Total, for example, to ingest 20 grams of dietary fiber. This is not meant to denigrate the usefulness of consuming a wide array of products which have appreciable fiber content. However, to produce 20 grams of dietary fiber from foods other than bran, one would have to eat any of the following: 400 grams of whole meal bread, 681 grams of carrots, 775 grams of cabbage or 1,477 grams of fresh apples

(Table 1). Therefore, unprocessed wheat bran is the most efficient means of dramatically increasing dietary fiber.[19,20]

Most patients with diverticulitis do not require surgical treatment. The major indications for such therapy are severe recurrent disease, colonic perforation and suspected carcinoma.[21] In persons who have a single severe bout of diverticulitis that requires admittance to hospital, surgical therapy is rarely necessary. Findings in one retrospective study indicated that a single bout of clinically severe diverticulitis does not necessarily predict recurrent bouts of disease.[22] Of the 134 patients admitted to Yale-New Haven Hospital for their first bout of severe diverticulitis, 99 patients were given medical therapy. Of these patients, 72 (73 percent) either did not require further admittance to hospital for recurrent diverticular symptoms or died of unrelated causes during the nine-year follow-up. Of 33 patients who had initial surgical treatment for diverticulitis, 26 (79 percent) did not have recurrent symptoms in the nine-year follow-up. Although patients were not chosen randomly for surgical or medical treatment groups and, thus, may not be truly comparable study groups, the data do suggest that if patients respond to inhospital medical therapy, recurrent attacks will not necessarily characterize the future course of the disease.

Diverticular hemorrhage is the most common identifiable cause of significant rectal bleeding. In one study from Atlanta, 20 percent of patients who were thoroughly examined had diverticula as the source of rectal bleeding.[23] In this study, 30 percent of patients who underwent extensive barium evaluations and colonoscopy, had no identifiable lesions observed. Colonic diverticula rarely bleed during the course of severe diverticulitis. Thus, diverticular hemorrhage does *not* usually occur as a part of the clinical syndrome of diverticulitis. Instead, in most instances of diverticular hemorrhage, the patient is otherwise in good health, presenting with hematochezia without any abdominal complaints, abdominal tenderness, fever or leukocytosis. The vascular anatomy of the diverticulum is such that most diverticula at formation have mesenteric arterioles arching over them (Figure 9). Recent pathological studies have documented that in patients in whom we can pinpoint the site of diverticular hemorrhage, eccentric intimal vascular changes can be observed (Figure 10).[24] On careful pathological evaluation, one can demonstrate the focal weakening of the vascular wall and, on occasion, the vascular perforation and thrombus extending into the lumen of the diverticulum. The problem with examining resected specimens is that there are no local inflammatory changes around the bleeding diverticulum at the time of pathological inspection. In a patient with known colonic diverticula, lower gastrointestinal hemorrhage cannot be assumed to be due to the diverticula. In the Atlanta series, for example, in 85 patients with diverticulosis who presented with significant colonic bleeding, 40 percent had other lesions on colonoscopy, including cancer, polyps and arteriovenous malformations of the right side of the colon.[23]

Another major problem for clinicians is determining the site of diverticular hemorrhage. Half of the bleeding colonic diverticula are located in the ascending colon, even though most colonic diverticula develop in the descending and sigmoid colon.[25] Therefore, many bleeding diverticula are right-sided whereas most cases of diverticulitis occur on the left. When trying to confirm the diagnosis of known or suspected diverticular hemorrhage, an initial anorectal examination is essential. This includes a careful rectal examination,

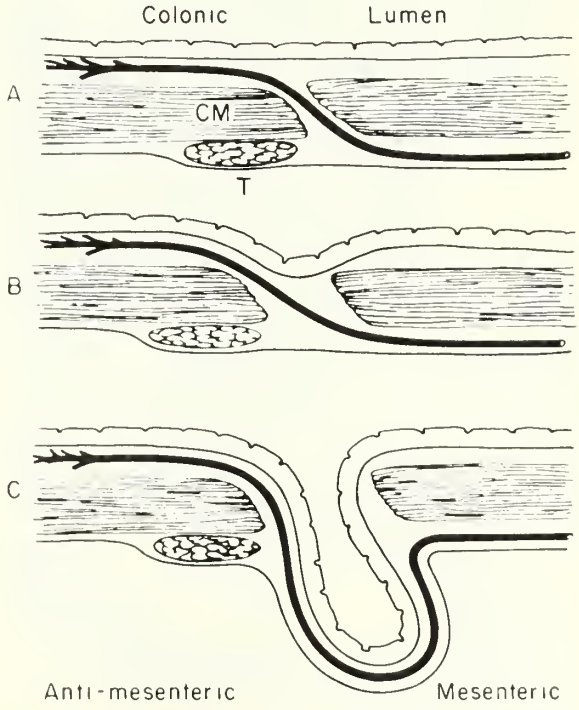


Figure 9.—Relationship of developing diverticulum to mesenteric arteriole. Arching over a diverticulum developing through an oblique gap in circular smooth muscle (CM), the mesenteric arteriole supplies colonic mucosal blood. (Reproduced with permission from Meyers et al.[24])

anoscopy and sigmoidoscopy, which should be negative in those with diverticular hemorrhage—aside from blood coming from above the rigid sigmoidoscope. An important point to consider is that a sizable number of patients with hematochezia, who are suspected of bleeding from a colorectal lesion, are bleeding from an upper gastrointestinal source. Therefore, in any patient where there is evidence of hematochezia and substantial volume loss (such as with hypotension or hyperactive bowel sounds), a nasogastric tube should be placed and gastric lavage undertaken. If there is blood in the lavage, or if there is no bilious material in the gastric lavage (thus, not sampling the postpyloric portion of the bowel), one should seriously consider upper endoscopic evaluation before carrying out an elaborate and invasive diagnostic series to investigate the lower bowel. In those patients who have negative gastric aspiration and proctosigmoidoscopy, further evaluation of the colon is determined by the briskness of hemorrhage. If significant hematochezia continues one should strongly consider angiography; however, this is likely to visualize a bleeding lesion only if hemorrhage is more than 0.5 ml per minute. If patients stop hemorrhaging, one should resist the temptation to proceed immediately with an emergency barium enema. The lack of good preparation with cathartics and enemas is liable to render the study inadequate. It is worthwhile to wait for 12 to 24 hours and then proceed with a barium contrast study if there has been no recurrence of bleeding. Should bleeding recur during the waiting period, one should do an arteriogram. Colonoscopy has only a limited role in patients with brisk bleeding, primarily because the vigorous hemorrhaging into the stool-filled colon presents great difficulties in conducting a thorough examination. Angiography in vigorous diverticular hemorrhage will identify a site of bleeding greater than 0.5 ml per minute. No unique vascular changes are noted in patients with diverticular hemorrhage; just contrast material filling the lumen of the colon at the site of hemorrhage (Figure 11). The site, but not the cause of hemorrhage is thus identified, a valuable piece of information should an operation become necessary.

Figure 10.—Bleeding site at the antimesenteric margin of the diverticulum. The ruptured vas rectum (VR), the arching mesenteric arteriole, has considerable internal thickening (arrow). A thrombus (T) has formed in the diverticular lumen (D). (Reproduced with permission from Meyers et al.[24])

Therapy for diverticular hemorrhage first demands vigorous attention to volume replacement. Vasopressin has been used extensively in patients with colonic hemorrhage.[25,26] Whether administered intravenously or intra-arterially, a substantial

Figure 11.—Mesenteric arteriogram in a patient bleeding from a diverticulum. Contrast material has collected in the lumen of the right colon. No abnormal vascularity is demonstrated.

decrease in mesenteric blood flow will occur. There is enhanced efficacy when it is administered intra-arterially, however.[27] Thus, in a patient who is bleeding vigorously from a colonic diverticulum, angiography can both localize the site of hemorrhage and be useful in initiating specific therapy. Usual dosages are 0.1 to 0.4 units of vasopressin per minute. Angiography also may be used for other forms of therapy, particularly in embolizing a bleeding vessel with Gelfoam or autogenous clot. This form of therapy has been most useful in acute illness in elderly patients who are poor surgical risks. However, as is the case with diverticulitis, the vast majority of patients who bleed from colonic diverticula do not require surgical therapy. Most of them require either no transfusions at all, or only blood transfusions, while about 20 percent require definitive surgical therapy.[28]

Conclusion

Diverticular disease of the colon is an extremely common human disorder, one which is almost certainly related to the introduction of modern food processing technology. Along with lung and colon cancer, hypertension and obesity, it is an unfortunate by-product of modern society.

REFERENCES

1. Majno G: The healing hand, chap 3, In Man and Wound in the Ancient World. Cambridge, Harvard University Press, 1975

2. Parks TG: Natural history of diverticular disease of the colon. Clin Gastroenterol 4:53-69, Jan 1975

3. Almy TP, Howell DA: Diverticular disease of the colon. N Engl J Med 302:324-331, Feb 1980

4. Gear JSS, Fursdon P, Nolan DJ, et al: Symptomless diverticular disease and intake of dietary fibre. Lancet 1:511-514, Mar 1979

5. Brodribb AJM, Humphreys DM: Diverticular disease: Three studies. Br Med J 1:424-430, Feb 1976

6. Burkitt DP: A deficiency of dietary fiber may be one cause of certain colonic and venous disorders. Am J Dig Dis 21:104-108, Feb 1976

7. Archampong EQ, Christian F, Badoe EA: Diverticular disease in an indigenous African community. Ann Royal Coll Surg Engl 60:464-470, Nov 1978

8. Segal I, Solomon A, Hunt JA: Emergence of diverticular disease in the urban South African black. Gastroenterology 72: 215-219, Feb 1977

9. Brodribb AJM, Condon RE, Cowles V, et al: Effect of dietary fiber on intraluminal pressure and myoelectrical activity of left colon in monkeys. Gastroenterology 77:70-74, Jul 1979

10. Brodribb J, Condon RE, Cowles V, et al: Influence of dietary fiber on transit time, fecal composition, and myoelectrical activity of the primate right colon. Dig Dis Sci 25:260-266, Apr 1980

11. Hodgson J: Diverticular disease. Am J Gastroenterol 62: 116-123, Aug 1974

12. Berman PM, Kirsner JB: Current knowledge of diverticular disease of the colon. Am J Dig Dis 17:741-759, Aug 1972

13. Boles RS, Jordan SM: The clinical significance of diverticulosis. Gastroenterology 35:579-582, Dec 1958

14. Shulman AG: High bulk diet for diverticular disease of the colon. West J Med 120:278-281, Apr 1974

15. Eastwood MA: Medical and dietary management. Clin Gastroenterol 4:85-97, Jan 1975

16. Eastwood MA, Smith AN, Brydon WG, et al: Comparison of bran, ispaghula, and lactulose on colon function in diverticular disease. Gut 19:1144-1147, Dec 1978

17. Hodgson WJB: The placebo effect—Is it important in diverticular disease? Am J Gastroenterol 67:157-162, Feb 1977

18. Brodribb AJM: Treatment of symptomatic diverticular disease with a high-fibre diet. Lancet 1:664-666, Mar 1977

19. Cummings JH, Branch W, Jenkins DJA, et al: Colonic response to dietary fibre from carrot, cabbage, apple, bran and guar gum. Lancet 1:5-9, Jan 1978

20. Hyland JMP, Taylor I: Does a high fibre diet prevent the complications of diverticular disease? Br J Surg 67:77-79, Feb 1980

21. Orebaugh JE, MaCris JA, Lee JF: Surgical treatment of diverticular disease of the colon. Am Surg 44:712-715, Nov 1978

22. Larson DM, Masters SS, Spiro HM: Medical and surgical therapy in diverticular disease. Gastroenterology 71:734-737, Nov 1976

23. Tedesco FJ, Waye JD, Raskin JB, et al: Colonoscopic evaluation of rectal bleeding. Ann Intern Med 89:907-909, Dec 1978

24. Meyers MA, Alonso DR, Gray GF, et al: Pathogenesis of bleeding colonic diverticulosis. Gastroenterology 71:577-583, Oct 1976

25. Lewis EE, Schnug GE: Importance of angiography in the management of massive hemorrhage from colonic diverticula. Am J Surg 124:573-580, Nov 1972

26. Baum S, Rosch J, Dotter CT, et al: Selective mesenteric arterial infusions in the management of massive diverticular hemorrhage. N Engl J Med 288:1269-1272, Jun 1973

27. Freedman AR, Kerr JC, Swan KG, et al: Primate mesenteric blood flow—Effects of vasopressin and its route of delivery. Gastroenterology 74:875-878, May 1978

28. McGuire HH, Haynes BW: Massive hemorrhage from diverticulosis of the colon: Guidelines for therapy based on bleeding patterns observed in fifty cases. Ann Surg 175:847-853, Jun 1972

Important Advances in Clinical Medicine

Epitomes of Progress — Obstetrics and Gynecology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in obstetrics and gynecology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in obstetrics and gynecology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Obstetrics and Gynecology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

The Prolactinoma Problem: Long-Term Issues and Short-Term Answers

A RECENT AUTOPSY SURVEY suggests that 10 percent of the population in the United States have prolactinomas. If true, prolactinomas have become the most frequent endocrine disorder, more common even than diabetes, yet little is known of their natural history. It is clear, however, that among a selected population of women with amenorrhea and infertility, as many as a third have hyperprolactinemia and, of these, a third have prolactinomas. Moreover, if galactorrhea is also present, hyperprolactinemia occurs in 75 percent of these patients, and the certainty of a tumor is doubled. Further, early diagnosis is very important because the duration of amenorrhea, for example, appears inversely related to therapeutic success. Because almost 65 percent of women with prolactinomas have a history of sustained exposure to estrogen (in pregnancy or from use of oral contraceptives), menstrual disorders in these women indicate the need for prompt screening for hyperprolactinemia.

Three forms of therapy are available to patients with prolactinomas. Pituitary irradiation, either by conventional radiation therapy or with alpha particles, has been discouraging thus far; only a few patients have had remission of symptoms and in most, serum prolactin (PRL) levels remain elevated as long as three years after treatment.

Bromocriptine mesylate (Parlodel), a dopamine receptor agonist, suppresses excessive secretion of PRL within several weeks in more than 85 percent of cases, although side effects limit prolonged use in 10 percent to 20 percent of patients. Nonetheless, this drug restores both menses and fertility and arrests galactorrhea with the same success rate as surgical procedures. The long-term effects on tumor growth remain unclear—some tumors have shown radiologic regression, whereas others, particularly those found in pregnant women, have increased in size. More important, cessation of bromocriptine is followed by prompt recurrence of hyperprolactinemia in 85 percent of patients. Bromocriptine therefore is best reserved for symptomatic improvement of hyperprolactinemia in patients without radiologic evidence of tumor and in those for whom operations have been unsuc-

cessful. When drug therapy is used as an alternative to operating to induce fertility, prolonged and perhaps lifetime surveillance may be needed to assess tumor growth.

Pituitary transsphenoidal microsurgery remains the preferred treatment for prolactinomas. Successful removal of microtumors with preservation of pituitary function is possible in up to 90 percent of cases. Restoration of menses and cessation of galactorrhea can be achieved in as many as 75 percent of patients, although PRL levels are restored to normal in only 50 percent of them. Finally, the minimal mortality and morbidity rates of this operation, when carried out by an experienced surgeon, indicate that it is the best treatment for prolactinomas available at present.

ERNEST M. GOLD, MD

REFERENCES

Burrow GN, Wortzman G, Newcastle NB, et al: Microadenomas of the pituitary and abnormal sellar tomograms in an unselected autopsy series. N Engl J Med 304:156-158, Jan 15, 1981

Schlechte J, Sherman B, Halmi N, et al: Prolactin secreting pituitary tumors in amenorrheic women: A comprehensive study. Endocrine Reviews 1:293-308, 1980

Post KD, Biller BJ, Adelman LS, et al: Selective transsphenoidal adenomectomy in women with galactorrhea-amenorrhea. JAMA 242:158-162, Jul 13, 1979

Richmond IL, Newton TH, Wilson CB: Prolactin-secreting adenomas: Correlation of radiographic and surgical findings. Am J Radiol 134:707-710, 1980

Tolis G: Prolactin: Physiology and pathology. Hosp Pract, pp 85-95, Feb 1980

Prenatal Diagnosis of Short-Limbed Dwarfism by Ultrasonography

ULTRASONOGRAPHY has greatly improved our ability to diagnose fetal malformations prenatally. Many anomalies of the fetal neural axis, bowel and kidneys have been described, and in the last two years considerable attention has been directed toward abnormalities of the fetal bony skeleton.

Ultrasonic diagnosis of short-limbed dwarfism is accomplished by measuring the length of the fetal femurs. The length of the femoral diaphysis, readily measured with real-time ultrasonographic systems, is compared with the biparietal diameter as an "internal" control of fetal size variability. Normal values have been established for femur lengths from the end of the first trimester to early third trimester and 99 percent confidence limits have been set.

In patients at risk for having babies with short-limbed bone dysplasias, we begin femur measurements at approximately 18 to 20 weeks after the last menstrual period (LMP). If the initial measurement falls within the normal range, serial measurements should be obtained at two-week intervals until either the femur length falls into the abnormal range or the 28th week is reached and normalcy is established.

Thus far, successful diagnoses have been established in fetuses before 22 weeks of age (based on LMP) in the Ellis-van Creveld syndrome, diastrophic dwarfism, achondrogenesis and homozygous achondroplasia. In addition, an unclassified but severe dwarf syndrome has been accurately predicted before 22 weeks menstrual age. Three cases of heterozygous achondroplasia were diagnosed but the presence of short femurs was not confirmed until after 24 weeks menstrual age. In eight patients at risk for having babies with dwarf syndromes, fetuses were diagnosed as showing no abnormalities and, subsequently, the diagnoses proved correct.

The most interesting observation in this series to date, other than the dramatic accuracy in this small sample of patients, is the fact that limb growth in dwarfs occurs differently in heterozygous achondroplasia than in homozygous achondroplasia or other more severe forms of dwarfism. Not only does this fact enable one to separate homozygous from heterozygous achondroplasia by a simple and safe examination, but it establishes differences in bone growth that were not previously recognized.

ROY A. FILLY, MD

REFERENCES

Mahoney MJ, Hobbins JC: Prenatal diagnosis of chondroectodermal dysplasia (Ellis-van Creveld syndrome) with fetoscopy and ultrasound. N Engl J Med 297:258-261, Aug 4, 1977

Filly RA, Golbus MS, Carey JC, et al: Short-limbed dwarfism: Ultrasonographic diagnosis by mensuration of fetal femoral length. Radiology, 1981 (In press)

Queenan JT, O'Brien GD, Campbell S: Ultrasound measurement of fetal limb bones. Am J Obstet Gynecol 138:297-302, Oct 1, 1980

Intrauterine Growth Retardation

THE DIAGNOSIS of intrauterine growth retardation (IUGR) is appropriate for any neonate whose birth weight is less than the tenth percentile for its gestational age. This aberration in growth may result from numerous causes, but the most common include maternal vascular disease, multiple gestations, chromosomal and other isolated malformations of the fetus and fetal viral infections.

Initially, the diagnosis is suspected when the uterine size is too small for the presumed gestational age of the fetus. Ultrasonographic evaluation

confirms the diagnosis by showing a decreased rate of growth of the fetal biparietal diameter and a decrease in the total intrauterine volume associated with oligohydramnios. More recently, concomitant measurements of head-to-body circumference ratios have proved helpful in delineating IUGR.

When it has been determined that an aberration in growth exists during pregnancy, management includes counseling of parents, consultation with a neonatologist and tests to evaluate fetal well-being. The latter include electronic monitoring of the fetal heart rate responses to fetal movement and to uterine contractions. If these responses are normal and maternal vascular disease is absent, the patient may continue her pregnancy to term. Consideration of delivery before term may be an option when fetal lung maturity has been achieved. Because poor oxygenation often results in birth asphyxia in these infants during labor, fetal heart rate monitoring is indicated; a cesarean section should be seriously considered.

A neonate with IUGR has a constellation of problems which may include birth asphyxia with its associated complications of meconium aspiration pneumonitis and central nervous system depression as well as hypoglycemia, hypocalcemia, temperature instability and polycythemia. Problems related to congenital malformations and infections also occur. Close observation to prevent birth asphyxia in the prepartum and intrapartum periods and intensive neonatal supportive care result in the best long-term outcome.

ROBERT RESNIK, MD

REFERENCES

Battaglia FC: Intrauterine growth retardation: An invitational symposium. J Reprod Med 21:283-286, Nov 1978

Jones MD Jr, Battaglia FC: Intrauterine growth retardation. Am J Obstet Gynecol 127:540-549, Mar 1, 1977

Levine SC, Filly RA, Creasy RK: Identification of fetal growth retardation by ultrasonographic estimation of total intrauterine volume. JCU 7:21-26, Feb 1979

Recent Advances in Prenatal Diagnosis of Genetic Defects

A SIGNIFICANT ADVANCE in medical genetics is the ability to make an in utero diagnosis of genetic defects. The study of amniotic fluid constituents allows the diagnosis of all chromosomal and many metabolic abnormalities. However, some disorders are not manifested by changes in amniotic fluid constituents. The development of fetoscopy and the ability to obtain fetal blood specimens makes possible prenatal diagnosis of diseases not possible by amniocentesis—among these are the hemoglobinopathies.

Since the first reports of the prenatal diagnosis of a hemoglobinopathy over 700 pregnancies have been monitored. Both structural abnormalities (such as sickle cell) and abnormalities of synthesis rates of globin chains can be diagnosed in utero. The risk of fetal death and spontaneous abortion from fetoscopy and fetal blood sampling is approximately 4 percent to 5 percent when done by an experienced physician.

Some cases of sickle cell anemia can be diagnosed in utero using only amniocentesis. These techniques involve use of restriction endonucleases, enzymes which cleave DNA within specific base-sequence recognition sites. There is an endonuclease-defined DNA mutation on the same chromosome as (but not part of or related to) the sickle mutation in 50 percent to 60 percent of American blacks carrying the sickle mutation. Therefore, in this proportion of the families at risk, a prenatal diagnosis can be accomplished with amniotic fluid cells (which contain DNA) instead of fetoscopic blood sampling.

MITCHELL S. GOLBUS, MD

REFERENCES

Kan YW, Dozy AM: Polymorphism of DNA sequence adjacent to human beta-globin structural gene: Relationship to sickle mutation. Proc Natl Acad Sci USA 75:5631-5635, Nov 1978

Alter BP: Prenatal diagnosis of hemoglobinopathies and other hematologic diseases. J Pediatr 95:501-513, Oct 1979

The Value of Microsurgery in Tubal Repair

THE MICROSURGICAL APPROACH has been applied to every form of tubal repair, but its value has been definitely established only in reversal of female sterilization. Microsurgery appears to be of some value in repair of salpingostomy in cases of chronic pelvic inflammatory disease in that it results in 25 percent to 30 percent intrauterine pregnancies; at the same time, however, it increases the rate of ectopic pregnancies from between 2 percent and 4 percent to between 10 percent and 18 percent. It is of technical value in implantation procedures, but in only one report has the technique improved the percentage of intrauterine pregnancies reaching term.

Success with reversal of sterilization largely depends on how the sterilization was originally done. Unipolar cautery yields the worst prognosis for reversal whereas use of a tubal clip appears to

allow the best. Bipolar cauterization, the Falope Ring and the Pomeroy techniques offer an intermediary prognosis. The site of anastomosis is also pertinent to prognosis. An anastomosis between the cornu-isthmus or isthmus-isthmus yields the best results (a pregnancy rate of 70 percent to 75 percent). Poorer results (a pregnancy rate of 45 percent to 55 percent) are obtained when the anastomosis involves the cornu-ampulla or ampulla-ampulla.

When microsurgical techniques are used to reverse sterilization, intrauterine pregnancy rates of 58 percent and 65 percent have been reported in large series of patients by Winston and Gomel, respectively. In a smaller series (47 patients) followed for more than 18 months, Gomel reported a pregnancy rate of 81 percent. By comparison, *macro*surgical techniques for reversal of sterilization have resulted in 21 percent to 37 percent pregnancy rates.

Despite variations in technique, it is evident that microsurgical procedures for the reversal of sterilization in women offer substantially improved results.

CARL J. LEVINSON, MD

REFERENCES

Daniel RK, Terzis JK: Reconstructive Microsurgery. Boston, Little, Brown, and Co, 1977

Winston RML: Reversal of tubal sterilization. Clin Obstet Gynecol 23: 1261-1268, Dec 1980

Gomel V: Microsurgical reversal of female sterilization: A reappraisal. Fertil Steril 33:587-597, Jun 1980

Antiprostaglandin Compounds in the Management of Primary Dysmenorrhea

WHILE THE EXACT incidence of dysmenorrhea is unknown, it appears to affect 30 percent to 50 percent of young women, causing them to lose time from work and school.

Primary dysmenorrhea occurs only in ovulatory cycles and is characterized by an absence of pelvic pathology and the presence of a variable number of systemic symptoms, including nausea, vomiting, diarrhea, headache, fatigue, dizziness and lower backache.

In the 1950's it was first suggested and subsequently proved that excessive prostaglandin action results in many of the symptoms of dysmenorrhea. In the early 1970's several papers were presented that indicated that nonsteroidal anti-inflammatory agents such as aspirin, indomethacin and naproxen, inhibited uterine contractions. Arachidonic acid is converted to prostaglandin through a number of steps. The first is the formation of a cyclic endoperoxidase. It is this step that is inhibited by the nonsteroidal anti-inflammatory drugs to prevent the production of excess prostaglandin.

A clearer understanding has been gained of the pathophysiology of dysmenorrhea and the efficacy of these inhibitors of prostaglandin synthesis in providing symptomatic relief, with the result that naproxen sodium and ibuprofen are among the drugs approved by the Food and Drug Administration for treatment of primary dysmenorrhea. Relief from symptoms is excellent for most patients, and these treatment compounds are well tolerated with minimal side effects. Most women who were formerly physically incapacitated by primary dysmenorrhea are now able to return to productive activity through use of these nonsteroidal anti-inflammatory compounds.

FREDERICK W. HANSON, MD

REFERENCES

Hanson FW, Izu A, Henzl MR: Naproxen sodium in dysmenorrhea: Its influences in allowing continuation of work/school activities. Obstet Gynecol 52:583-587, Nov 1978

Henzl MR: A new perspective on dysmenorrhea: The role of prostaglandins and prostaglandin inhibitors. J Reprod Med 25 (Suppl):191-242, Oct 1980

A New and Effective Treatment of Hirsutism

HIRSUTISM, an androgen-dependent manifestation of accelerated hair growth, occurs in women having either ovarian or adrenal overproduction of androgens or hypersensitivity of hair follicles to androgenic stimulation (idiopathic hirsutism). In the past, satisfactory medical treatments have not been available. Recently, however, an understanding of the role of androgenic receptors in hair follicles combined with the characterization of several compounds that have antiandrogenic properties have afforded a new approach in the treatment of hirsutism.

Spironolactone (Aldactone), an aldosterone agonist, currently used as a diuretic and in the treatment of mild hypertension, has been found to possess several antiandrogenic properties. It has the ability to inhibit the cytochrome P-450 enzyme systems, which are required for the biosynthesis of androgens (by way of hydroxylation) in both the gonadal and adrenal steroid-producing cells and, consequently, result in reduced androgen secretion. It also inhibits the androgenic action of testosterone and its 5α-reduced metabolite, 5α-

dihydrotestosterone by occupying the binding sites of cytosol and nuclear receptors in all target tissues including hair follicles. Thus, the combined inhibitory effects on androgen production and action of spironolactone make it an ideal pharmacological agent for the treatment of hirsutism. Clinical trials by us and others have demonstrated that spironolactone reduces facial hair growth within three months with remarkable efficiency. A dosage regimen of 25 to 100 mg per day of spironolactone reduced testosterone and androstenedione production by 30 percent to 60 percent. Spironolactone is equally effective in idiopathic hirsutism and hirsutism due to ovarian androgen excess, such as in the polycystic ovary syndrome. These observations are consistent with the peripheral and glandular sites of action. Further, we have shown that the inhibition of androgen production is selective upon ovarian steroidogenesis and not upon adrenal steroidogenesis, which is an important consideration for long-term administration of spironolactone. In the long-term treatment (up to 16 months) of 30 patients during the past four years, we have not observed any significant side effects. Thus, it would appear that spironolactone is a safe and effective drug in the treatment of hirsutism.

S. S. C. YEN, MD

REFERENCES

Boisselle A, Tremblay RR: New therapeutic approach to the hirsute patient. Fertil Steril 32:276-279, Sep 1979

Shapiro G, Evron S: A novel use of spironolactone: Treatment of hirsutism. J Clin Endocrinol Metab 51:429-432, Sep 1980

Cumming DC, Yang JC, Rebar RW, et al: Treatment of hirsutism with spironolactone: Endocrine and clinical effects. JAMA, 1981 (In press)

Severe Cardiovascular Complications Associated With β-Sympathomimetic Tocolysis and Their Prevention

TRANSIENT MYOCARDIAL ischemia, cardiogenic pulmonary edema and fatal myocardial insufficiency have been reported in association with β-sympathomimetic therapy for inhibition of preterm labor. The incidence of such severe cardiovascular complications is not known for most of these agents but is estimated to range from less than 1 percent for intravenously administered isoxsuprine (Vasodilan) to 5 percent for terbutaline (Brethine, Bricanyl) given intravenously. Because the causes of these complications are unknown, it is important to recognize several clinical features that characterize the development of cardiovascular compromise in these patients:

- Marked increase in cardiac work resulting from increased stroke volume and heart rate.
- The presence of multiple fetuses, which is known to be accompanied by increased plasma volume and cardiac output values.
- Excessive administration of fluids (crystalloids in particular) in the presence of fluid and sodium retention, resulting in decreased hematocrit and colloid osmotic pressure. This fluid retention is thought to be caused by activation of the renin-aldosterone axis.
- Hypokalemia without increased urinary potassium secretion, indicative of a shift of potassium into the intracellular compartment.
- Prolonged therapy—for at least 24 hours in most cases.
- Absence of correlation between the rate of drug administration and the development or severity of symptoms. Most patients have been treated with drug doses in the lower half of the accepted therapeutic spectrum.
- Prompt resolution of signs and symptoms after discontinuation of the drug, with or without induced diuresis.

Recently, the first β-sympathomimetic agent was approved by the Food and Drug Administration for use in the treatment of preterm labor; therefore, more patients will be exposed to possible severe adverse cardiovascular side effects of the drug. Physicians should include the following measures in the clinical management of patients receiving β-sympathomimetic tocolytic therapy:

- Monitor cardiovascular signs and symptoms frequently, especially in patients with multiple fetuses.
- Observe fluid balance carefully by accurately recording fluid intake and output as well as patient's daily weight (restrict fluid intake if fluid is retained).
- Avoid prolonged tachycardia (>140 beats per minute).
- If abnormal signs and symptoms develop, carry out tests such as an electrocardiogram, roentgenogram of the chest and echocardiogram before continuing therapy.
- Obtain baseline and follow-up blood specimens to monitor hemoglobin, hematocrit and electrolyte concentrations in patients receiving intravenous therapy.

β-Sympathomimetic drugs are useful in attempting to inhibit preterm labor; however, occasional cardiovascular complications may occur. In most patients, increased awareness, preventive measures, early diagnosis and prompt therapy will result in a good outcome.

MICHAEL KATZ, MD

REFERENCES

Jacobs MM, Knight AB, Arias F: Maternal pulmonary edema resulting from beta-mimetic and glucocorticoid therapy. Obstet Gynecol 56:56-59, Jul 1980

Katz M, Robertson PA, Creasy RK: Cardiovascular complications associated with terbutaline treatment for preterm labor. Am J Obstet Gynecol 139:605-608, Mar 1981

Chlamydial Infections in Obstetrics and Gynecology

Chlamydia trachomatis has been identified as a major sexually transmitted pathogen in industrialized countries. It is estimated that there are 3 million cases of chlamydial infection occurring annually in the United States. *C trachomatis* is an obligatory intracellular bacterium that depends on the infected host cell for nutrients and energy. There are 15 known serotypes of *C trachomatis;* serotypes D,E,F,G,H,I and K are involved in eye, genital tract and perinatal infections.

The cervix is the site most commonly infected with *C trachomatis* in the female genital tract. A patient may be asymptomatic or may have endocervicitis with a mucopurulent discharge and hypertrophic ectropion.

Inclusion conjunctivitis of newborns has been recognized since the first decade of this century. However, it was not until the late 1970's, with the impetus of the report by Beam and Saxon, that extraocular chlamydial infections in infants were recognized. It is now clear that inclusion conjunctivitis of newborns is not a rarity, but probably the most common form of conjunctivitis seen in the first month of life, and that chlamydial pneumonia of infants is one of the relatively common causes of pneumonia in the first six months of life. An infant born to a woman with a chlamydial infection of the cervix is at 60 percent to 70 percent risk for acquiring infection during passage through the birth canal. In approximately 25 percent to 50 percent of exposed infants conjunctivitis will develop and in approximately 10 percent to 20 percent of the infants pneumonia will occur. Transplacental transmission is not known to occur. Chlamydial conjunctivitis is not prevented by application of silver nitrate drops. Treatment consists of administration of erythromycin, tetracycline ointment or sulfa drops. The recommended treatment for chlamydial pneumonia in infants is 40 mg of erythomycin per kg of body weight, given in four divided doses for 14 days.

Preliminary studies have suggested that pregnant women from whom *C trachomatis* organisms have been recovered have a significantly increased risk for the development of late-onset endometritis following vaginal delivery. A possible role for *C trachomatis* in spontaneous abortion, fetal deaths, and preterm labor and delivery has also been suggested.

When considering chlamydial infections of the female genital tract, the only laboratory test that is useful in routine diagnosis is isolation of *C trachomatis* in susceptible tissue culture cell lines. This requires access to a virology laboratory. Cytology is not successful in diagnosing cervical infections because of limited sensitivity. Serological testing is not useful in detecting lower genital tract infections because of high background prevalence rates of antichlamydial antibodies in sexually active populations. However, it may be useful in systemic disease, such as salpingitis, or pneumonia in newborns. The serological test of choice remains the microimmunofluorescent test of Wang and Grayston.

RICHARD L. SWEET, MD

REFERENCES

Schachter J: Chlamydial infections. N Engl J Med 298:428-435, 490-495, 540-549, Feb 23, Mar 2, Mar 9, 1978

Richmond SJ, Oriel JD: Recognition and management of genital chlamydial infection. Br Med J 2:480-483, Aug 12, 1978

Mardh P-A, Ripa T, Svensson L, et al: *Chlamydia trachomatis* infection in patients with acute salpingitis. N Engl J Med 296: 1377-1379, Jun 16, 1977

Ovarian Carcinoma: In Vitro Testing of Sensitivity to Chemotherapy

THE PHARMACOLOGY of cancer cells in humans, including mechanisms of resistance and methods of predicting drug activity, is being tested in vitro by a stem cell assay. Thus, ovarian carcinoma, a tumor with clinically demonstrated sensitivity to a variety of antineoplastic agents, can be studied by the use of disaggregated cells from fresh operative specimens or malignant effusions that are suspended in 3 percent agar in an enriched medium. Tumor stem cells, which are responsible for the continued growth of metastatic lesions, form

colonies (collections of more than 40 cells) in the medium within 10 to 21 days.

Drugs to be tested for activity against ovarian carcinoma are added to the cell suspension in three different concentrations. After an hour, the cells are washed and prepared for culture. Colonies from a control and three treated media are counted after 14 days through an inverted phase microscope to determine drug effect.

A quantitative sensitivity index of tumor stem cells to each drug can be determined graphically from linear curves that compare drug concentration with colony survival. For each drug, a limit of sensitivity is selected on the basis of preliminary experimental data, and tumors are classified as sensitive if the area under the curve does not exceed the chosen limit.

Patterns of drug activity in vitro can be correlated with subsequent clinical response and tumor specimens can be obtained serially in some patients, providing an opportunity to study the development of drug resistance. It is hoped that the stem cell assay can be used as an initial guide to appropriate chemotherapy and, also, can obviate the need for treatment with toxic drugs to which the tumor is insensitive. To date, the assay appears predictive of response in about 65 percent of cases and of resistance in about 90 percent.

SAMUEL C. BALLON, MD

REFERENCES

Hamburger AW, Salmon SE: Primary bioassay of human tumor stem cells (a). Science 197:461-463, Jul 29, 1977

Salmon SE, Hamburger AW, Soehnlen B, et al: Quantitation of differential sensitivity of human-tumor stem cells to anti-cancer drugs. N Engl J Med 298:1321-1327, Jun 15, 1978

Alberts DS, Chen HSG, Soehnlen B, et al: In vitro clonogenic assay for predicting response of ovarian cancer to chemotherapy. Lancet 2:340-342, Aug 16, 1980

Two Mechanisms of Late Decelerations: Reflex and Myocardial Hypoxia

THE CURRENT THEORY that late decelerations are due to fetal hypoxia and are, therefore, ominous, does not explain a number of clinical observations. For example, (1) infants born after a prolonged series of late decelerations, even up to several hours in some cases, are not necessarily depressed (low Apgar scores) or acidotic provided fetal heart rate (FHR) variability has been maintained. (2) Infants born after a positive oxytocin challenge test (or contraction stress test) are not necessarily depressed or acidotic at birth. (3) Early decelerations are thought to be due to fetal head compression. The presumed mechanism is a transient change in cerebral blood flow resulting in vagal discharge due to hypoxia. However, such infants are not depressed or acidotic.

Recent animal experimentation, clinical observation and a review of some decades-old human fetal data support the belief that late decelerations are of two types.

Reflex late decelerations, the first type, are seen when a sudden acute insult, such as maternal hypotension, is superimposed on a previously normally oxygenated fetus. These late decelerations are caused by a decrease in uterine blood flow (with the uterine contraction) that makes it impossible for the fetus to extract sufficient oxygen. The deoxygenated blood is carried from the fetal placenta, through the umbilical arteries to the heart and distributed to the aorta, neck vessels and head. Here the low oxygen tension is sensed by chemoreceptors, and neuronal activity results in a vagal discharge that causes the transient deceleration. The deceleration may be late because of the circulation time from the fetal placental site to the chemoreceptors. Between contractions, oxygen delivery is adequate.

These late decelerations are accompanied by normal FHR variability and, thus, signify normal central (for example, the brain or heart) oxygenation; that is, the fetus is physiologically compensated. Centralization of the fetal circulation, a well-recognized fetal response to moderate asphyxia, results from vasoconstriction of nonpriority organs, such as muscle and gut, and increase or maintenance of blood flow to the vital organs, such as the brain, heart and placenta.

Early decelerations, which are mild in depth and usually associated with normal FHR variability, most likely result from the same mechanism as the reflex vagal late decelerations just described.

The second type of late deceleration is initiated in the same manner as the first type except that the deoxygenated bolus of blood from the placenta is also insufficient to support myocardial action. Direct myocardial hypoxic depression as well as vagal activity result. This type of deceleration is seen with more prolonged asphyxia and is recognized by decreased or absent FHR variability, which signifies fetal decompensation—that is, inadequate fetal cerebral and myocardial oxygenation. This condition is seen most commonly in states of decreased placental reserve, such as preeclampsia, intrauterine growth retardation or following pro-

longed stress (for example, prolonged severe variable or late decelerations).

The first type of late deceleration is best described as a stress pattern, which is usually reversible by appropriate treatment, such as maintenance of maternal blood pressure, avoidance of excessive uterine activity, lateral position to maximize placental blood flow and maternal hyperoxia. The second type of late deceleration should be described as a sinister pattern that requires rapid attempts to alleviate it and, if this fails, expeditious delivery of the fetus.

J. T. PARER, MD, PhD

REFERENCES

Martin CB Jr, de Haan J, van der Wildt B, et al: Mechanisms of late decelerations in the fetal heart rate—A study with autonomic blocking agents in fetal lambs. Europ J Obstet Gynec Reprod Biol 9:361-373, Dec 1979

Parer JT, Krueger TR, Harris JL: Fetal oxygen consumption and mechanisms of heart rate response during artificially produced late decelerations of fetal heart rate in sheep. Am J Obstet Gynecol 136:478-482, Feb 15, 1980

ADVISORY PANEL TO THE SECTION ON OBSTETRICS AND GYNECOLOGY

EUGENE SANDBERG, MD
Advisory Panel Chairman
CMA Scientific Board Representative
Stanford University

JOSEPH A. OLIVER, MD
CMA Section Chairman
Pasadena

W. GORDON PEACOCK, MD
CMA Section Secretary
San Francisco

ALAN KING, MD
Loma Linda University

KENNETH NISWANDER, MD
University of California, Davis

PHILIP DISAIA, MD
University of California, Irvine

J. G. MOORE, MD
University of California, Los Angeles

WILLIAM E. LUCAS, MD
University of California, San Diego

DONALD MINKLER, MD
University of California, San Francisco

DANIEL R. MISHELL, MD
University of Southern California
Los Angeles

EZRA DAVIDSON, JR, MD
Charles R. Drew Postgraduate School of Medicine
Los Angeles

J. WILLISON ALLEN, MD
Sacramento

THOMAS G. MOYERS, MD
San Diego

JACK HALLATT, MD
Long Beach

TONIA M. MARRALLE, MD
Newport Beach

GERALD TROBOUGH, MD
Los Gatos

ROBERT N. SMITH, MD
Section Editor
San Francisco

EDITORIALS

Of Gluts and Prices

WE ARE TOLD in the news media that we now have a glut of oil. It is also said that soon we will have a glut of doctors. The conventional expectation is that competition in the free market will bring about lower prices which, in turn, will lower fuel and health care costs. But one has an uncomfortable feeling that this will happen slowly, if at all. Certainly, at this writing there has been no great plummeting of gasoline prices for consumers as a result of the oil glut.

One wonders how free the free market really is. There is much in our system that supports prices and even increases them notwithstanding a glut. The prices of goods or services, whether these be gallons of gasoline or health care services, are closely tied to the cost of producing them, and also, though less directly, to whatever the market will bear. The former costs are governed to a substantial degree by such things as union contracts for pay and working conditions for those who produce the goods or services, and to the sometimes needed and sometimes not-so-needed requirements imposed by government regulations. Neither union contracts nor government rules respond easily or quickly to gluts. What the market will bear also depends in part on how essential the goods or services in question may be, as well as on the degree of the glut or extent of the scarcity. Obviously, those that are essential will more readily be paid their asked price, particularly if they are also scarce.

It seems likely that the free market, whether for oil or medical services, is not as free in reality as it may be in theory. Those in government and elsewhere who are depending on it to reduce costs soon and significantly may be disappointed.

—MSMW

Iron Nutrition

OCCASIONALLY it is worthwhile to reexamine our understanding of common diseases in which the medical diagnosis and treatment appear to be well developed. Elsewhere in this issue, Dallman summarizes new information concerning iron deficiency, particularly in young children and pregnant women whose iron balance is precarious. Such recent studies provide a better basis for examining certain general issues relating to iron balance in humans.

The first step is the *recognition* of iron deficiency. For clinicians the diagnosis begins with anemia, and the more specific diagnosis of iron deficiency is established by methods that monitor iron status. These laboratory studies have different characteristics and somewhat different implications. Perhaps the most prominent difference is the limited ability of red cell indices, red cell protoporphyrin and transferrin saturation tests to separate iron deficiency from inflammatory disease. This separation is effectively accomplished by the serum ferritin determination.[1] The importance of defining iron deficiency accurately in an anemic patient is, of course, in the subsequent detection of its cause as much as in the treatment of the deficiency per se.

But what about the much larger population whose iron deficiency—here defined as a decrease in essential body iron—may be said to be nutritional? It is surprising how poor our data are on the prevalence of iron deficiency. This is more from an error in methodologic approach than anything else. It has been customary to use hemoglobin values to separate normality from iron deficiency, even though we know the overlap between anemia and normality determinations is enormous. Indeed, in surveys where hemoglobin is used as the initial criterion, evidence would suggest that only half of the population called anemic are below their physiological norm, whereas approximately half of those with iron deficiency go unrecognized.[2] There are good methods for confirming iron deficiency, including

transferrin saturation, red cell protoporphyrin and serum ferritin values, and these tests must be used in population studies if affected persons are to be accurately identified. Hemoglobin concentration remains the practical means for evaluating the severity of iron deficiency but not its presence.

An educated guess of the prevalence of iron deficiency on a global basis is about 15 percent, with a prevalence in developed countries of about half that.[3] Most of the deficiency is concentrated in vulnerable populations, that is, among menstruating and pregnant women and in children. Nutritional iron deficiency in the United States is usually mild, and one might wonder whether this disorder, which affects perhaps 15 million people, is of any concern. There may never be a completely informed answer to this question, which focuses particularly on the effects of iron deficiency on tissues. Biochemical and functional abnormalities are being identified, but their importance in persons with a mild deficiency will be difficult to estimate. Should iron deficiency then be left to physicians to detect and treat, or is the maintenance of an adequate iron balance a public health problem?

The explanation for the high prevalence of iron deficiency in humans appears to lie in the peculiarities of iron absorption from food.[4] Using a per kilo basis of comparison with other animal species, humans have an iron intake one or two orders of magnitude less. While some animals absorb nonheme iron better than heme iron, humans absorb heme iron better. It would seem that humans are genetically endowed with a capacity to use iron from animal sources. Unfortunately, changes have occurred in our diet, and to some extent we are victims of our own ingenuity. The cultivation of grain, the reduction in iron contamination of foods and the reduction in caloric intake have made it more difficult to maintain iron balance especially during periods of growth, menstruation and pregnancy. In a sense our present diet is at odds with our genetic endowment with respect to iron absorption.

In considering a solution to this problem, the opposite problem of iron overload must also be examined. Recent methods, including particularly transferrin saturation and plasma ferritin, have made it possible to screen a population for parenchymal iron overload.[5] Current estimates of the number of persons with a parenchymal iron load of 10 grams or more vary considerably, but a reasonable estimate would be 0.1 percent. Tissue damage will occur in only a fraction of these persons. However, measures taken to ameliorate iron deficiency might well exaggerate the iron load and result in tissue damage among more persons. What, then, should be the general approach to these two disorders of iron metabolism? They might each be regarded as problems to be detected by clinicians at the time when they become sufficiently severe to show tissue damage or organ dysfunction. Or, individual solutions could be sought for each. The best solution to the problem of iron deficiency is nutritional engineering designed to increase the availability and absorption of dietary iron. In genetic disorders such as idiopathic hemachromatosis and thalassemia, the altered regulation of iron absorption leads to iron overload despite a normal diet. This infrequent problem will be effectively controlled only through better detection and more effective management.

CLEMENT A. FINCH, MD
Professor and Head
Division of Hematology
University of Washington School of Medicine
Seattle

REFERENCES

1. Jacobs A, Worwood M: Ferritin in serum—Clinical and biochemical implications. N Engl J Med 292:951-956, 1975

2. Cook JD, Finch CA, Smith NJ: Evaluation of the iron status of a population. Blood 48:449-455, 1976

3. Bothwell TH, Charlton RW, Cook JD, et al: Iron Metabolism in Man. Oxford, Blackwell, 1979

4. Cook JD, Finch CA: Iron nutrition. West J Med 122:474-481, 1975

5. Edwards CQ, Carroll M, Bray P, et al: Hereditary hemochromatosis: Diagnosis in siblings and children. N Engl J Med 297:7-13, 1977

Is There Miscommunication About Private Practice?

THIS WRITER has long had an uncomfortable feeling that many of the public may not understand the words private practice to mean what they mean to the medical profession. The meaning is clear enough to physicians, as are the meanings of the words intrusion and invasion when they are used in connection with private practice. But sometimes a suspicious nonprofessional public seems not really to appreciate why it is that physicians are so protective of what they call private practice and why they are so defensive of it against any intrusion or invasion. This might at least partially explain why there is not stronger or more obvious support for private practice by the public than seems to be the case.

Miscommunication can come about when the same words carry different messages to different

people, possibly because they may have different points of reference or simply because most of us have a tendency to see only what we want to see and to hear only what we want to hear. One cannot help wondering whether some of the nonprofessional public may be getting a different message when the medical profession speaks of private practice and deplores intrusions and invasions by government and others. The words themselves can suggest that something is being protected or maybe even hidden from outside interference or even outside awareness. After all, the word private can carry messages such as keep out, it's none of your business; intrusions can imply entry where one is not welcome; and the word invasion implies a more forceful effort at overcoming resistance to an unwanted entry. In each instance there is a suggestion that something is being protected and there can be a suspicion or uneasiness that whatever this is may be more likely in the professional than the public interest. Crassly it might be suspected that what is being protected is the financial interests of physicians.

It is certainly true that something is being protected under the rubric of private practice, and although physicians know exactly what they think this is, they seldom describe or define it publicly. Rather they seem to assume it as a given. For the record this writer believes that what doctors are actually trying to protect is something very central to the practice of medicine—that is, a physician's ability and freedom to provide what he or she believes to be the best possible care for each individual patient. This is fundamentally an individual matter between each physician and each patient, and any outside interference is regarded as an intrusion or invasion into something that is at the heart of good patient care and good medical practice.

It is entirely possible that words such as private, intrusion and invasion may too often be heard differently by the public than they are spoken by the profession. If this is so, then they do not serve us well. However, they are firmly entrenched in the medical lexicon and this is not likely to change. But what can be done is for the profession, in its dialogue with the public, to be much more direct, articulate and, above all, repetitive in stating exactly what it is they are trying to protect and preserve when they speak of the private practice of medicine and unwanted intrusions and invasions. There is nothing really being hidden. If so it will surely out. Somehow the real truth needs to come through much more clearly than it seems to now. The profession needs the public's support, and suspicions because of miscommunication are unnecessary and can only be destructive.

—MSMW

CASE REPORTS

Refer to: Faris MR, Skeen WF, Abrahams LA: Toxic shock syndrome in a 19-year-old woman. West J Med 134:535-539, Jun 1981

Toxic Shock Syndrome in a 19-Year-Old Woman

MARY RACHEL FARIS, MD
WILLIAM F. SKEEN, MD, MPH
LISA A. ABRAHAMS, BA
San Francisco

TOXIC SHOCK SYNDROME has received much publicity in the lay press as more cases have been recognized and reported. It is known that this illness can have serious sequelae such as shock, cardiopulmonary depression and death. We report a case of toxic shock syndrome in a 19-year-old woman in whom bibasilar pneumonia developed early in her illness, a manifestation of the syndrome not previously described. In reviewing the available literature on this syndrome and the entity known as adult Kawasaki disease, it seems that they have many clinical features in common. Some cases of adult Kawasaki disease may, in fact, represent toxic shock syndrome.

Report of a Case

A 19-year-old woman (gravida 0, para 0, abortus 0) was admitted to hospital complaining of sore throat, fever, watery diarrhea, headache and weakness for two days. On the day before admission a macular, erythematous, nonpruritic rash had developed on her face, arms, legs and trunk. A nonodorous vaginal discharge, present for three days preceding admission, had never occurred before. The patient had been seen the previous day at a different emergency room, where a throat culture had been done; she had been given an intramuscular injection of Bicillin (solution containing benzathine penicillin G and procaine penicillin G) at that time.

Her last menstrual period had begun nine days before admission and had ended three days before. She described it as normal except that she had used tampons for the first time; they were used night and day.

Her past medical history and family history were unremarkable except for a sister who had had scarlet fever during childhood.

On admission her blood pressure was 80/40 mm of mercury, pulse 172 and respirations 20 per minute, and temperature 39.8°C (103.6°F). The patient was pale, weak and cooperative. There was no conjunctival injection. Tympanic membranes were clear. Her tongue was denuded, beefy red and tender, as in a strawberry tongue. The posterior pharynx was injected, with bilateral tonsillar enlargement. There was no lymphadenopathy. The lungs were clear. The heart was tachycardic without murmur or gallop. There was some right upper quadrant abdominal tenderness, but there were no palpable abdominal organs. On rectal examination, no abnormalties were found. A pelvic examination, however, disclosed tender, erythematous perineum with a thick whitish discharge on the labia minora. The vaginal mucosa was denuded and erythematous. There was tenacious greenish discharge in the posterior fornix. The cervix was grossly inflamed and tender to touch and mobilization, without apparent discharge from the os. The uterus was small, anteverted and slightly boggy. The adnexa were less tender, with normal ovaries. The extremities showed indurative edema of hands and lower legs. Findings of a neurological examination were normal. A diffuse erythematous macular rash had developed in large patches on fingers, face, arms, legs and groin; it also involved palms and soles. There was no petechial, papular, hemorrhagic or pruritic component to the rash.

Laboratory examination disclosed a leukocyte count of 15,000 per cu mm, with 52 percent segmented neutrophils and 38 percent bands; hematocrit was 36.6 percent. Platelet count was 145,000 per cu mm. Serum sodium was 129 and potassium 3.1 mEq per liter; creatinine 2.4 and blood urea nitrogen (BUN) 51 mg per dl. SGOT (serum aspartate aminotransferase) was 59 units, glucose 137 mg per dl, lactic dehydrogenase (LDH) 164 IU per liter, serum calcium 7.7 mg per dl,

From St. Mary's Hospital & Medical Center, San Francisco.
Submitted, revised January 19, 1981.
Reprint requests to: Mary Rachel Faris, MD, St. Mary's Hospital & Medical Center, 450 Stanyan Street, San Francisco, CA 94117.

ABBREVIATIONS USED IN TEXT

BUN = blood urea nitrogen
CDC = Center for Disease Control
LDH = lactic dehydrogenase
TSS = toxic shock syndrome

albumin 3.3 grams per dl and total protein 5.5 grams per dl. Prothrombin time, partial thromboplastin time, amylase and creatine phosphokinase values were normal; antistreptolysin (ASO) titer was negative. Fibrin degradation products were less than 40 μg per ml (normal less than 20). Analysis of urine showed occult blood (2+), proteinuria (1+), 25 to 30 leukocytes and 5 to 8 erythrocytes per high-power field, with a few bacteria and a negative culture. Gram stain of vaginal discharge showed Gram-positive cocci in clusters and many pus cells; culture showed heavy growth of coagulase-positive *Staphylococcus aureus*. An electrocardiogram showed sinus tachycardia with nonspecific T-wave abnormalities. An x-ray study of the chest showed prominent pulmonary vascularity without infiltrates or effusions (Figure 1). Two sets of blood cultures (anaerobic and aerobic) as well as throat cultures obtained at the previous emergency room visit and admission to this hospital were negative.

Figure 1.—Chest roentgenogram showing prominent pulmonary vascularity without infiltrates or effusions.

The patient was admitted to hospital and vigorously resuscitated with saline solution at 250 ml per hour. She was treated with 1.2 million units of penicillin given intravenously every six hours for two doses, at which time therapy was changed to 1 gram of intravenously given nafcillin every four hours. Within 24 hours the fever had abated; the BUN value dropped to 11 with creatinine 0.9 mg per dl. However, she remained hypotensive and tachycardic and subjectively unimproved. Her fluid intake was slowed to 200 ml per hour. On the third hospital day the rash began to fade with membranous desquamation beginning on the fingertips and progressing to include palms, soles and face. Fluid intake was further slowed to 125 ml per hour. Blood pressure was 100/70 mm of mercury and pulse 84 beats per minute. Auscultation of the lungs and a chest roentgenogram showed the presence of small bilateral pleural effusions and perihilar edema, and bilateral alveolar infiltrates of the lower lobes were shown with air bronchograms (Figure 2). Findings of a cardiac examination remained unchanged. Leukocyte count was 7,100 per cu mm, with 51 percent segmented neutrophils and 30 percent bands. Arterial blood gas determinations were pH 7.41, partial pressure of oxygen (Po_2) 56 and partial pressure of carbon dioxide (Pco_2) 33 mm of mercury, and bicarbonate 21 mEq per liter. The patient was given supplemental oxygen. Diagnostic thoracentesis was carried out, disclosing straw-colored fluid with 10,900 erythrocytes and 790 leukocytes per cu mm (50 percent polymorphonuclear cells and 50 percent monocytes), with LDH 124 IU per liter, glucose 104 mg per dl, protein 1.2 grams per dl. Aerobic and anaerobic cultures were negative.

The presumptive diagnosis of pneumonia was made. In addition, it was felt that some of the edema and effusion were attributable to volume overload; the parenteral fluids were therefore decreased. The patient continued to receive nafcillin intravenously throughout her hospital course and exhibited gradual improvement with stable vital signs, continued desquamation where the rash had been, and resolution of the pleural effusions, infiltrates and pelvic symptoms. Her leukocyte count on the fifth hospital day was 8,600 per cu mm, with 66 percent segmented neutrophils and 2 percent bands. She was discharged on the eighth hospital day with no medications. It was recom-

mended that a follow-up vaginal culture be done as an outpatient.

Discussion

Toxic shock syndrome (TSS) has a sudden onset marked by high fever, watery diarrhea and vomiting, and is often accompanied by sore throat, headache and myalgias. A diffuse, macular, erythematous rash develops on the palms and soles and may include the face, trunk and groin. Subsequent membranous desquamation begins on the tips of the fingers and toes and spreads to the palms and soles. Sometimes, a nonpurulent conjunctivitis occurs. Within 48 hours, hypotension and shock ensue; urine output often decreases. In some cases, adult respiratory distress syndrome, cardiac dysfunction, acute tubular necrosis and disseminated intravascular coagulation have been observed.[1-3]

Multiorgan system involvement is reflected by abnormal findings on laboratory studies, including elevated levels of urea nitrogen, serum creatinine, bilirubin and creatine phosphokinase, and leukocytosis with a pronounced shift to the left. Platelet counts, which are low early in the disease, are usually elevated by the second week.[1] In addition, the Center for Disease Control (CDC) reports that positive cervical or vaginal cultures for *Staphylococcus aureus* were obtained in 16 of 17 cases (94 percent) before the initiation of antibiotic therapy.[1] A second series reported isolation of the same pathogen in cultures from the throat, cervix, vagina or rectum in 33 of 45 (73 percent) patients.[2] The prevalence of *S aureus* in the cervix or vagina of menstruating women without TSS is not known but is estimated to be in the range of 2 percent to 15 percent.[4]

Figure 2.—Chest roentgenogram showing small bilateral pleural effusions, perihilar edema and bilateral infiltrates of the lower lobes.

At least 95 percent of suspected cases of TSS reported to the CDC have occurred in women. The mean age is about 25 years, with a range of 13 to 52 years. Of the 40 female patients from whom a menstrual history was obtained, in 38 (95 percent) the disease began within five days from the beginning of menses. In all of the cases illness developed within ten days from the onset of menses.[2]

A case control study conducted by the CDC showed that all of 50 patients (100 percent) used tampons during menstruation compared with 43 of 50 controls (86 percent). In addition, more patients than controls used tampons day and night throughout menses. Both differences were statistically significant.[4]

In a study of 24 patients who had at least two menstrual periods since their first episode of TSS, the Wisconsin state health department found that 10 (42 percent) had at least one recurrence. Those patients who received β-lactamase-resistant penicillins or cephalosporins during their first episode had a substantially lower risk of recurrence than those patients who received neither drug.[4]

Treatment of these patients is supportive. They require large amounts of fluid and, frequently, need intensive care. β-Lactamase-resistant antibiotics have not been shown to influence the course of the disease or the outcome, although the risk of recurrence is reduced.[4] Mortality from TSS ranges from 3 percent to 15 percent.[2]

Concerned patients should be advised that they can almost entirely eliminate the risk of TSS by not using tampons. Alternatively, the risk may be reduced by using tampons during only part of the menstrual period and by avoiding high-absorbency brands. Women who have had TSS should not

use tampons until cultures have shown that *S aureus* has been eradicated from the vagina.[1]

All of the essential signs and symptoms for diagnosis of the disease were manifested by the case in point. The criteria for case definition as outlined by the CDC are (1) temperature greater than or equal to 38.8°C (102°F); (2) erythematous macular rash with desquamation; (3) systolic blood pressure of less than or equal to 90 mm of mercury for an adult; (4) involvement of at least four organ systems, and (5) lack of evidence for meningococcemia, Rocky Mountain spotted fever or bacteremia.[1]

The development in this patient of radiologic and clinical findings consistent with bilateral pneumonia and pleural effusions has not been reported previously. These pulmonary findings may represent an additional toxic manifestation of the disease. Early noncardiogenic pulmonary edema was considered less likely in the face of an elevated pleural fluid leukocyte count and pleural fluid/serum LDH ratio.

Characteristic findings at pelvic examination have not yet been identified as part of the syndrome. Our patient, however, was noted to have a bright erythematous rash involving the vulva and a purulent vaginal discharge. Similar findings have been described in another case reported as adult Kawasaki disease.[5] Noteworthy is the fact that our patient used tampons, for the first time, during the menses immediately preceding onset of the disease. This fact supports the preliminary epidemiologic data linking tampon use and TSS.

The differential diagnosis of TSS commonly includes two other disease entities, scarlet fever and Kawasaki disease. Many patients in whom TSS develops, including the present case reported, are initially diagnosed as having scarlet fever and are given penicillin therapy. The rashes produced by the two diseases may be similar, although the rash of scarlet fever does not involve the palms and soles. Desquamation of the palms and soles occurs in both diseases.[6] Penicillin therapy will be effective in patients with scarlet fever. In a patient with TSS, however, throat cultures should be negative for group A β-hemolytic streptococci, and the disease will run a more severe course with progression to hypotension and shock.

Recently, a number of suspected cases of adult Kawasaki disease have been reported.[5,7-10] Kawasaki disease and TSS appear to share many features —fever, conjunctivitis, desquamative rash, pharyngitis, diarrhea and various laboratory abnormalities. Nonetheless, significant differences exist. Classically, Kawasaki disease has been described in children less than 5 years of age.[6] The fever of Kawasaki disease lasts from one to two weeks, whereas that of TSS appears to be of shorter duration. The skin changes of both syndromes typically include a macular erythematous rash that is prominent on the palms and soles, face, trunk and groin. Subsequent desquamation of the rash begins at the junction of the nails and skin. In patients with Kawasaki disease a transverse furrow in the nails often develops one to two months after the onset of the disease.[6] This change, however, has not been described in patients with TSS. In both illnesses, indurative edema of the hands and feet may be pronounced.[6]

The complications of the two illnesses are different. Although unusual in Kawasaki disease, hypotension and shock are common features of TSS.[2] The cardiovascular sequelae of Kawasaki disease, however, are prominent. Approximately 70 percent of these patients have evidence of myocarditis or pericarditis. Sudden death occurs in 1 percent to 2 percent from coronary thrombosis or aneurysm. The pathological findings at autopsy of these patients are consistent with those of periarteritis nodosa.[6] Such findings have not been described in cases of TSS.

It is of interest that most of the cases reported as adult Kawasaki disease have occurred in females 16 to 27 years of age.[5,7-10] Several patients had severe dehydration and hypotension; one patient was noted to have a vaginal culture positive for *S aureus*.[5] Vaginal cultures were not mentioned in the other case reports. Two patients experienced multiple episodes of the illness at intervals of four weeks and coincident with menses.[7,10] All of the cases manifested sinus tachycardia; one patient had evidence of a transient pericardial effusion,[10] but no serious cardiac sequelae were reported. It seems likely that these cases actually represented TSS rather than an adult version of Kawasaki disease.

Summary

A 19-year-old woman was admitted to hospital with rash, hypotension and malaise. The diagnosis of toxic shock syndrome was made. Subsequently, bilateral pneumonia developed with pleural effusions, a finding not previously described. Her condition was similar to that of several other cases recently reported in the literature as adult Kawasaki disease.

REFERENCES

1. Richmond JB: Advisory on toxic-shock syndrome. FDA Drug Bull 10:10-11, 1980
2. Toxic-shock syndrome—United States. Morbidity Mortality Weekly Rep 29:229-230, May 23, 1980
3. Toxic-shock syndrome linked to tampon use. Intern Med Alert 2:33-34, 1980
4. Follow-up on toxic-shock syndrome—United States. Morbidity Mortality Weekly Rep 29:297-299, Jun 27, 1980
5. Lee TJ, Vaughan D: Mucocutaneous lymph node syndrome in a young adult. Arch Intern Med 139:104-105, 1979
6. Kawasaki T, Kosaki F, Okawa S, et al: A new infantile acute febrile mucocutaneous lymph node syndrome (MLNS) prevailing in Japan. Pediatrics 54:271-276, 1974
7. Snell GI: Adult Kawasaki disease—Three occurrences in the same patient. West J Med 132:548-549, Jun 1980
8. Everett DE: Mucocutaneous lymph node syndrome (Kawasaki disease) in adults. JAMA 242:542-543, 1979
9. Schlossberg D, Kandra J, Kreiser J: Possible Kawasaki disease in a 20-year-old woman. Arch Dermatol 115:1435-1436, 1979
10. Milgrom H, Palmer EL, Slovin SF, et al: Kawasaki disease in a healthy young adult. Ann Intern Med 92:467-470, 1980

Refer to: Meyer R, Jacobson I B: Control of refractory ventricular ectopy—Atrial and ventricular overdrive pacing. West J Med 134:539-544, Jun 1981

Control of Refractory Ventricular Ectopy

Atrial and Ventricular Overdrive Pacing

ROY MEYER, MD
LESTER B. JACOBSON, MD
San Francisco

THE SUPPRESSION of ventricular arrhythmias by cardiac pacing was first reported by Zoll and coworkers,[1] who used transcutaneous thoracic ventricular pacing to prevent the onset of ventricular tachycardia (VT) and ventricular fibrillation (VF) in patients with *complete* atrioventricular (AV) block and *slow* ventricular rhythms. Four years later Sowton and colleagues[2] reported the successful suppression of VT and VF in patients with *normal* AV conduction and *normal* ventricular rates by right ventricular endocardial pacing at rates exceeding the spontaneous sinus rate. During the past 15 years it has been clearly shown that ventricular[3-6] and atrial[6-9] pacing may be valuable techniques for suppressing otherwise intractable ventricular arrythmias that occur in circumstances involving myocardial ischemia,[3] cardiac operation[3,4] and medications that produce arrhythmias,[3,5] as well as in the absence of underlying heart disease.[7]

ABBREVIATIONS USED IN TEXT

AV = atrioventricular
LV = left ventricular
PAW = pulmonary artery wedge (pressure)
PVC = premature ventricular complex
VA = ventriculoatrial
VF = ventricular fibrillation
VT = ventricular tachycardia

Despite a large body of information on the hemodynamic effects of cardiac pacing in *stable* patients with and without heart disease, the hemodynamic effects of cardiac pacing in *unstable* patients with serious ventricular arrhythmias have not been adequately described, most likely because most reports on overdrive suppression were published before the availability of simple techniques for bedside hemodynamic monitoring. This case report illustrates the use of temporary atrial and ventricular pacing for overdrive suppression of serious ventricular arrhythmias in a patient several weeks after acute myocardial infarction. It documents and compares the changes in cardiac output and pulmonary artery wedge (PAW) pressure that occurred with suppression of the arrhythmia by atrial and ventricular pacing, as well as by antiarrhythmic medication.

Report of a Case

A 54-year-old man had an acute myocardial infarction during which pathological Q waves appeared in leads V_{1-4} and serum creatine kinase levels reached a peak of 3,252 IU per ml (normal 50 to 180 IU per ml). His initial hospital course was complicated by premature ventricular complexes (PVC's), which resolved following intravenous administration of lidocaine, and hypotension, which resolved with intravenous administration of modest amounts of fluids. After 15 days in hospital the patient was discharged with instructions to take propranolol, 20 mg four times a day, because he was having intermittent chest discomfort that suggested myocardial ischemia. In the ensuing two weeks severe shortness of breath developed to the point where he had orthopnea, and he began to be aware of abnormal cardiac activity. He was readmitted to hospital and found to be in severe congestive heart failure and to have

From the Division of Cardiology, Presbyterian Hospital of Pacific Medical Center, San Francisco. Dr. Jacobson is now at the San Francisco Kaiser Foundation Hospital.

Submitted, revised, May 22, 1980.

Reprint requests to: Roy Meyer, MD, Division of Cardiology, Presbyterian Hospital, P.O. Box 7999, San Francisco, CA 94120.

frequent multiform PVC's, occasionally as many as four in a row. Initial treatment with sequential intravenous administration of large doses of lidocaine and procainamide did not alter the arrhythmia, so 20 mg of propranolol every six hours and 200 mg of disopyramide (Norpace) every eight hours were administered orally. However, the additional medication did not suppress the arrhythmia. Within 36 hours of starting the propranolol and disopyramide therapy, the congestive heart failure state became more profound, and a Swan-Ganz thermodilution catheter was inserted. The mean pulmonary artery wedge pressure measured 28 mm of mercury, so diuretics were administered intravenously. The patient was transferred to Pacific Medical Center for evaluation and treatment.

On admission, the patient looked and felt very weak. He appeared to have moderately low cardiac output with moderate jugular venous distention and diffuse rales that suggested high intracardiac filling pressures. There was a large area of anterior wall dyssynergy and a prominent S_3 gallop. An electrocardiogram (ECG) (Figure 1) showed abnormalities compatible with the recent anterior wall myocardial infarction and multiform PVC's singly, in pairs and in short runs. About 60 percent of the QRS complexes were PVC's. The initial mean PAW pressure was 19 mm of mercury, and cardiac output determined in triplicate by the thermodilution technique was 2.8 liters per minute (cardiac index = 1.5 L/min/m^2). Laboratory values for serum electrolytes, creatinine, creatine kinase and blood urea nitrogen were within normal limits. The liver function tests showed mild abnormalities compatible with hepatic congestion.

Because the PVC's had persisted despite the addition of large doses of intravenously given lidocaine, the decision was made to attempt to suppress them with pacing techniques. Therefore, a 4F bipolar electrode catheter was introduced percutaneously into a left antecubital vein and, using electrocardiographic monitoring (with the pin from the tip electrode attached to the V1 terminal of the ECG machine) advanced to an area in which the atrial electrogram was very prominent (Figure 2). Consistent atrial capture from this area was achieved with a current output of about 2 mamp using the Medtronic Model 5880A external pacemaker generator. As shown in Figure 3A, asynchronous atrial pacing was initiated at a rate of about 105 per minute, and the rate was gradually increased until ventricular ectopic activity was consistently suppressed, which occurred at an atrial rate of about 125 beats per minute. However, as shown in Figure 3B, at rates slightly below 120 beats per minute ventricular ectopic activity reappeared. After 30 minutes of atrial pacing at a rate of about 125 beats per minute, there was a dramatic increase in cardiac output from 2.9 to 4.8 liters per minute and a fall in the mean PAW pressure from 19 to 14 mm of mercury. Figure 4 displays a plot of cardiac output against mean PAW pressure to display the serial hemodynamic changes that occurred as a result of changes in cardiac rhythm.

In an attempt to suppress the PVC's with antiarrhythmic medications, quinidine sulfate and phenytoin (Dilantin) were administered orally

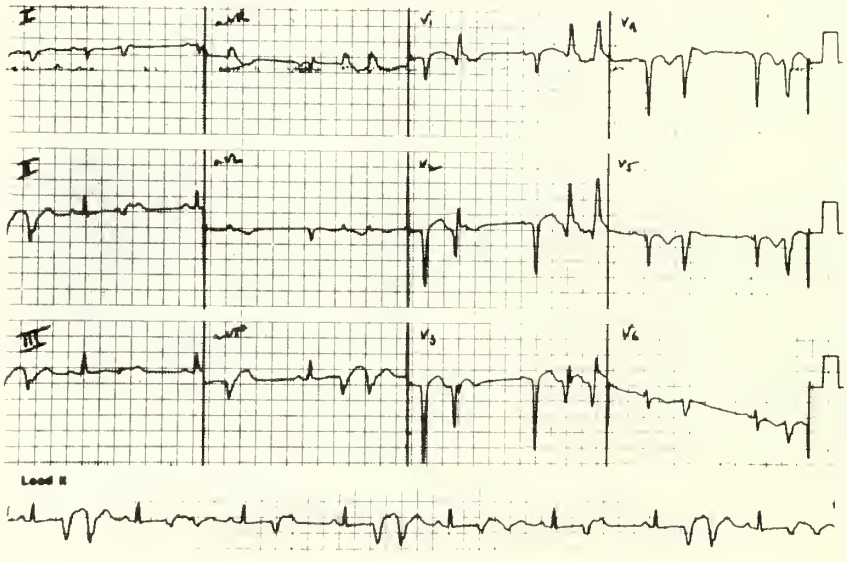


Figure 1.—Twelve-lead electrocardiogram showing PVC's and abnormalities compatible with the recent anterior wall myocardial infarction. The lead II rhythm strip displays the frequency and group beating pattern of PVC's (PVC's = premature ventricular complexes).

while atrial pacing was continued at a rate of about 125 beats per minute. Within hours after these medications had been given, the initially suppressed PVC's reappeared in a bigeminal pattern, as their coupling intervals became progressively shorter than the paced atrial cycle length.

Although PVC's could be completely suppressed at this time by increasing the atrial pacing rate to slightly more than 130 beats per minute, the pacing rate was kept at about 125 beats per minute and the bigeminal rhythm allowed to occur. Serial measurements during atrial pacing indicated that the cardiac output was lower in the presence of the PVC's than in their absence and, at identical PAW pressures of 10 mm of mercury, the cardiac output was higher when the PVC followed a paced P wave than when it occurred almost simultaneously with it (4.5 versus 4.1 liters per minute).

To see the effect of the antiarrhythmic medication alone on the spontaneous rhythm, pacing was stopped briefly every two hours. Atrial pacing was discontinued after 28 hours when stable sinus rhythm with only rare PVC's were present. An hour after cessation of atrial pacing, the cardiac output was 3.9 liters per minute and the mean PAW pressure was 12 mm of mercury. The dramatic rise in cardiac output and the fall in mean PAW pressure between the initial and final points in Figure 5 reflect solely the beneficial effects of suppression of the PVC's.

Over several days the patient increased his activities and felt reasonably well. Cardiac catheterization, left ventricular cineangiography and selective coronary arteriography were done to assess the advisability of operative intervention. The findings showed significant left ventricular

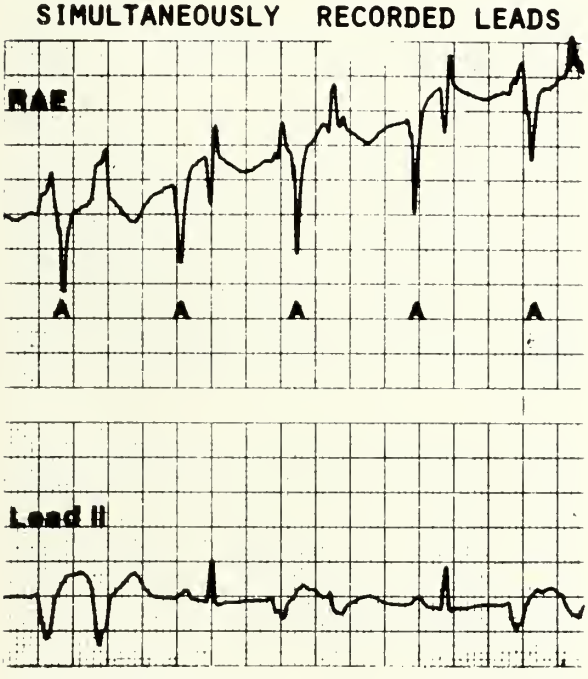


Figure 2.—Simultaneously recorded unipolar right atrial electrogram (RAE) and lead II. The RAE is recorded in the area from which atrial pacing was carried out (A = atrial deflections).

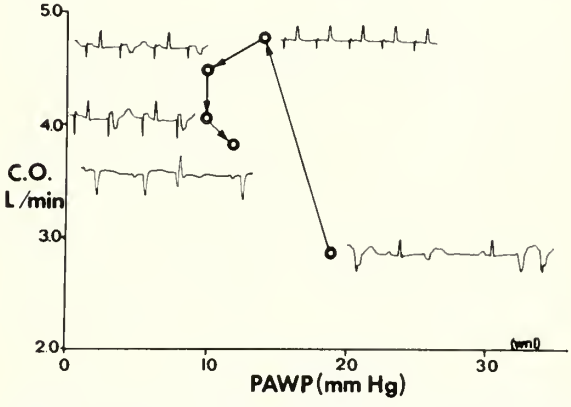


Figure 4.—Display of serial changes in cardiac output (C.O.) and mean pulmonary artery wedge pressure (PAWP) with changes in rhythm during therapy. The increase in C.O. and the fall in mean PAWP between the initial and final points reflect the beneficial effects of suppression of PVC's by antiarrhythmic medications (PVC's = premature ventricular complexes).

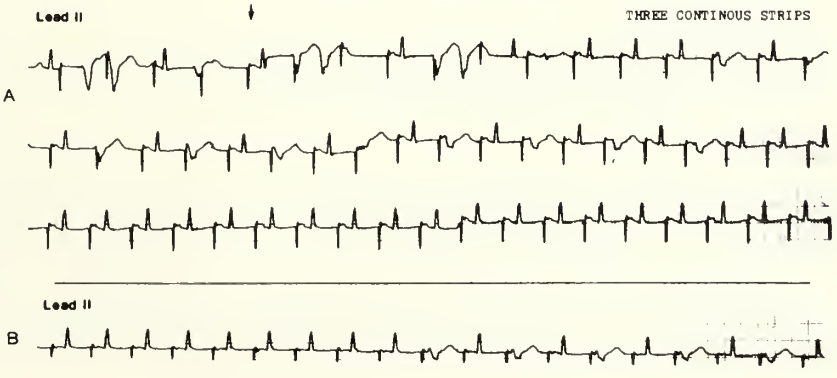


Figure 3.—**A,** Three continuous lead II rhythm strips recorded as atrial pacing is initiated and the pacing rate increased. Consistent atrial capture begins at the arrow. Complete suppression of PVC's occurs at a paced atrial rate of about 125 beats per minute. **B,** As the atrial pacing is slowed from 125 to 118 beats per minute the PVC's reappear (PVC's = premature ventricular complexes).

(LV) dysfunction with a very large LV end-diastolic volume, large anterior, apical and septal dyskinetic segments, a mildly elevated LV end-diastolic pressure of 14 mm of mercury, and a severely reduced calculated ejection fraction of 0.36. The cardiac output, determined by the dye dilution technique, was 4.4 liters per minute and the aorta-right atrial oxygen difference was 4.9 ml per dl when the rhythm was sinus at a rate of 90 per minute with rare PVC's. Selective coronary arteriography showed total occlusion of the proximal portion of the left anterior descending coronary artery, but in the remaining branches of the left coronary artery system and the entire right coronary artery system no abnormalities were noted. It was felt that LV aneurysmectomy was not indicated because the arrhythmia was adequately controlled with medication, and inadvisable because the interventricular septum, which appears to play an important role in postmyocardial infarction ventricular arrhythmias,[10] could not have been resected. The patient was discharged with instructions to take 1,000 mg of quinidine per day (which had resulted in a plasma quinidine level of 3.2 mg per liter) and 300 mg of phenytoin per day.

At home the patient resumed his usual sedentary activities and did well for about five weeks until he suffered an unheralded cardiac arrest. He was resuscitated by paramedics who found him to be in ventricular tachycardia, which they terminated with direct current countershock. Following cardioversion the rhythm was sinus with frequent PVC's which could not be suppressed despite intravenous administration of lidocaine, procainamide, propranolol and phenytoin. So, using a temporary bipolar electrode catheter introduced into the right internal jugular vein and located with its tip probably in the middle coronary vein, demand ventricular pacing was initiated at a rate of about 80 beats per minute; the rate gradually increased to about 110 per minute, at which time suppression of almost all PVC's was achieved. At this point the patient was transferred back to Pacific Medical Center. There had been no evidence of acute myocardial necrosis at the time of the cardiac arrest.

On readmission the patient was weak and seemed to have moderately low cardiac output with high intracardiac filling pressures. The systemic pressure was variable but averaged about 95/60 mm of mercury during a paced ventricular rhythm at a rate of about 110 beats per minute. During ventricular pacing there was AV dissociation with occasional sinus capture beats because the sinus rate was about 92 per minute and no ventriculoatrial (VA) conduction was present. A Swan-Ganz thermodilution catheter was introduced into the left internal jugular vein and passed to the pulmonary artery. The mean PAW pressure was 21 mm of mercury, the cardiac output was substantially reduced at 2.2 liters per minute (cardiac index = 1.2 L/min/m^2), and the AV oxygen difference was substantially widened at 10.7 ml per dl. The severity of the ventricular arrhythmia (Figure 5) precluded discontinuing ventricular pacing long enough to measure cardiac output and PAW pressure during spontaneous rhythm.

Although ventricular pacing was clearly suppressing ventricular ectopy, its use was associated with a very poor hemodynamic state even though there was no VA conduction at this time. Therefore, an attempt was made to carry out atrial pacing with a 4F bipolar electrode catheter introduced into a superficial arm vein and passed into the right atrium. Despite consistent atrial capture, complete suppression of the PVC's did not occur at rates as high as 145 beats per minute because of the short coupling intervals of the PVC's. Thus,

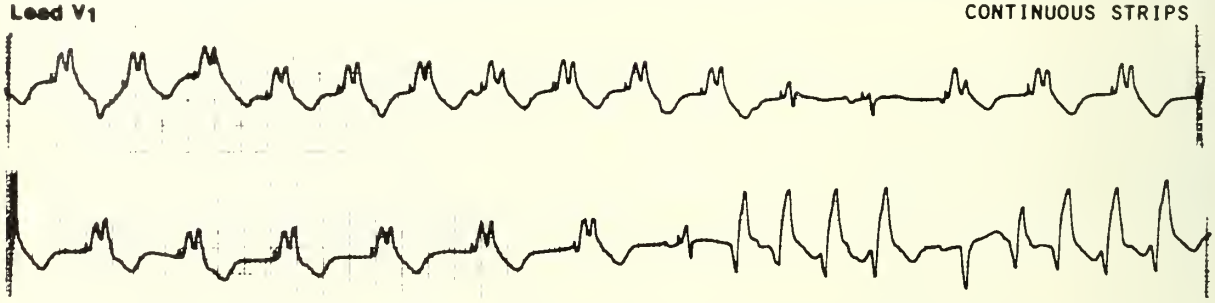


Figure 5.—Two continuous lead V_1 rhythm strips recorded as the rate of ventricular pacing is decreased from about 113 beats per minute. When the paced ventricular rate reaches about 76 beats per minute salvos of PVC's appear (PVC's = premature ventricular complexes).

ventricular pacing at 110 per minute was continued while 300 mg per day of phenytoin was given. The dosage of quinidine sulfate was increased from 1,000 to 2,400 mg per day to achieve higher therapeutic plasma levels. During ventricular pacing the cardiac output ranged from 2.2 to 2.9 liters per minute and the mean PAW pressure stabilized at 17 to 18 mm of mercury. Ventricular pacing was continued for 14 days, until spontaneous PVC's did not occur during sinus rhythm. In the ten days following discontinuation of ventricular pacing, the patient was able to walk about the hospital with only rare PVC's, without angina pectoris and with adequate control of congestive heart failure. He was discharged with instructions to take 300 mg per day of phenytoin and 2,400 mg per day of quinidine sulfate. Over eight months he has continued do do well.

Discussion

This case illustrates the value of cardiac pacing as a temporizing measure in the control of ventricular ectopic activity, and shows that pacing the atrium or the ventricle may be equally effective in this regard. Furthermore, it shows the considerable hemodynamic improvement that may occur with atrial overdrive pacing and documents the superiority of atrial over ventricular pacing in optimizing the hemodynamic state in a patient with LV dysfunction. The dramatic rise in cardiac output and the fall in mean PAW pressure that occurred with atrial overdrive suppression in this patient are not attributable to an increase in heart rate, for the average ventricular rate before atrial pacing was about 120 beats per minute (Figure 1), similar to the ventricular rate during atrial pacing. Rather, this dramatic hemodynamic improvement reflects (1) the suppression of ventricular ectopic beats which occur at such short coupling intervals that the abbreviated diastolic filling time results in low end-diastolic volume and, thus, small stroke volume on the basis of the Frank-Starling mechanism, and (2) preservation of the normal atrial and ventricular contraction sequences which, in the setting of LV dysfunction, may have a profoundly beneficial effect on LV stroke volume.[11] The fact that during ventricular bigeminy at identical PAW pressures of 10 mm of mercury the cardiac output was higher when the PVC followed a paced P wave than when it occurred almost simultaneously with it indicates that the coupling interval of a PVC may be of hemodynamic significance by virtue of its relationship to atrial contraction as well as its absolute degree of prematurity.

In this patient the beneficial effects of a properly timed atrial contraction on cardiac output are demonstrated by the substantially higher cardiac output (4.8 versus 2.2 to 2.9 liters per minute) during atrial pacing than during ventricular pacing at comparable rates and at comparable LV filling (mean PAW) pressures. While the rapid ventricular rates required to reduce ventricular ectopic activity might be expected to reduce cardiac output, it is clear from this and other reports[12] that cardiac output may not fall at high pacing rates and that at any given pacing rate the hemodynamic changes will depend on the chamber (atrium versus ventricle) paced,[12] the degree of suppression of ventricular ectopic activity achieved and the coupling intervals of the PVC's to the spontaneous QRS complexes. Furthermore, growing evidence suggests that the theoretical risk of inducing myocardial ischemia with rapid pacing has been overestimated because the rapid pacing rates have generally been well tolerated by patients with coronary artery disease and myocardial ischemia.[3,13] Often, the addition of antiarrhythmic medications allows the pacing rate required for suppression of PVC's to be lowered, even if such drugs were not initially effective in completely suppressing the arrhythmias.[6] Similarly, an arrhythmia resistant to either pacing at an acceptable rate or to antiarrhythmic medication alone may respond to the simultaneous use of both therapeutic modalities.[7]

Atrial pacing is the preferred mode of suppressing ventricular ectopic activity because it provides the hemodynamic advantage of atrial and ventricular synchrony which, in turn, allows rapid ventricular rates to be achieved without hemodynamic deterioration. However, when its use is precluded by the presence of atrial standstill, flutter and fibrillation, ventricular pacing may be effectively employed. In the presence of sinus rhythm with high grade AV block, AV sequential pacing would be expected to be the preferred modality[14] and might, during our patient's second hospital stay, have provided hemodynamic improvement in addition to PVC suppression.

Achieving consistent atrial capture at low-energy output for longer than several hours is often not possible when pacing is carried out, as was the case in our patient, with the electrode catheter tip floating freely within the right atrium.

Therefore, when it is anticipated that atrial pacing will be needed for prolonged periods of time, it is preferable to position fluroscopically specially designed electrode catheters into the coronary sinus or right atrial appendage.

It is unclear in our patient's case whether improvement in the hemodynamic state per se played a role in the suppression of the PVC's; however, the fact that PVC's were completely abolished with ventricular pacing at a rate of 110 beats per minute at a time when the cardiac output was very low and the mean PAW pressure was 17 to 18 mm of mercury, suggests that hemodynamic improvement is *not necessary* for the effective suppression of ventricular ectopic activity by overdrive pacing. This observation and the conclusion of a recent review article[13] suggest that the phenomenon of overdrive pacing may be explained on a purely electrophysiological basis. However, as the exact mechanisms responsible for ventricular ectopic activity in humans are still uncertain, the mechanisms by which rapid pacing suppresses ventricular arrhythmias remain unclear. Early workers, believing that ventricular ectopic activity reflected enhanced automaticity, hypothesized that rapid pacing evoked changes in electrolyte and autonomic milieu, events that depress automaticity by increasing the stimulation threshold and by reducing the rate of spontaneous depolarization and the amplitude of the action potential of an ectopic focus.[13,15] More recent reports, advocating reentry as the mechanism of ventricular ectopic activity, suggest that rapid pacing suppresses ventricular ectopic activity by causing changes in conduction velocities and in refractory periods of tissues making up the reentrant pathways.[16,17] However, as many patients successfully treated with rapid pacing have had long QTU intervals before pacing,[4,5,8,9,18-20] it is possible that the phenomenon of overdrive suppression involves rate-related shortening of the Purkinje fiber action potential.

Conclusions

Overdrive pacing for the suppression of ventricular arrhythmias may be an effective temporizing measure employed to allow time for adequate levels of antiarrhythmic medications in the blood and tissues to be achieved or for an acute process such as drug effect, myocardial ischemia or infarction to resolve. However, for patients with recurrent life-threatening ventricular arrhythmias, long-term overdrive suppression may be achieved with permanent atrial and ventricular pacing systems.[2,6-8,18] Although this technique has not received much attention in recent literature, it deserves reemphasis as a valuable therapeutic modality which may have dramatic antiarrhythmic and beneficial hemodynamic effects in specific clinical situations.

Summary

Temporary atrial and ventricular pacing was carried out to suppress refractory ventricular arrhythmias in a patient in whom acute myocardial infarction had occurred several weeks earlier. Although pacing from both locations was effective in suppressing ventricular arrhythmias, atrial pacing provided greater hemodynamic improvement.

REFERENCES

1. Zoll PM, Linenthal AJ, Zarsky LRN: Ventricular fibrillation—Treatment and prevention by external electrical currents. N Engl J Med 262:105-112, 1960

2. Sowton E, Leatham A, Carson P: The suppression of arrhythmias by artificial pacing. Lancet 2:1098-1100, 1964

3. Beller BM, Kotler MN, Collens R: The use of ventricular pacing for suppression of ectopic ventricular activity. Am J Cardiol 25:467-473, 1970

4. Eraklis AJ, Green WT Jr, Watson CG: Recurrent paroxyms of ventricular tachycardia following mitral valvuloplasty. Ann Surg 161:63-66, 1965

5. Schoonmaker FW, Osteen RT, Greenfield JC Jr: Thioridazine (Mellaril®) induced ventricular tachycardia controlled with an artificial pacemaker. Ann Intern Med 65:1076-1078, 1966

6. Zipes DP, Wallace AG, Sealy WC, et al: Artificial atrial and ventricular pacing in the treatment of arrhythmias. Ann Intern Med 70:885-896, 1969

7. Cohen LS, Buccino RA, Morrow AG, et al: Recurrent ventricular tachycardia and fibrillation treated with a combination of beta-adrenergic blockade and electrical pacing. Ann Intern Med 66:945-949, 1967

8. DeFrancis NA, Giordano RP: Permanent epicardial atrial pacing in the treatment of refractory ventricular tachycardia. Am J Cardiol 22:742-745, 1968

9. Kastor JA, DeSanctis RW, Harthorne JW, et al: Transvenous atrial pacing in the treatment of refractory ventricular irritability. Ann Intern Med 66:939-945, 1967

10. Josephson ME, Harken AH, Horowitz LN: Endocardial excision: A new surgical technique for the treatment of recurrent ventricular tachycardia. Circulation 60:1430-1439, 1979

11. Ogawa S, Dreifus LS, Shenoy PN, et al: Hemodynamic consequences of atrioventricular and ventriculoatrial pacing. PACE 1:8-15, 1978

12. Samet P, Castillo C, Bernstein WH: Hemodynamic sequelae of atrial, ventricular and sequential atrioventricular pacing in cardiac patients. Am Heart J 72:725-729, 1966

13. Haft JI: Treatment of arrhythmias by intracardiac electrical stimulation. Prog Cardiovasc Dis 16:539-568, 1974

14. Hartzler GO, Maloney JD, Curtis JJ, et al: Hemodynamic benefits of atrioventricular sequential pacing after cardiac surgery. Am J Cardiol 40:232-236, 1977

15. DeSanctis RW, Kastor JA: Rapid intracardiac pacing for treatment of recurrent ventricular tachyarrhythmias in the absence of heart block. Am Heart J 76:168-174, 1968

16. El-Sherif N, Scherlag BJ, Lazzara R, et al: Re-entrant ventricular arrhythmias in the late myocardial infarction period—I. Conduction characteristics in the infarction zone. Circulation 55: 686-702, 1977

17. El-Sherif N, Hope RR, Scherlag BJ, et al: Re-entrant ventricular arrhythmias in the late myocardial infarction period—II. Patterns of initiation and termination of re-entry. Circulation 55: 702-719, 1977

18. Loeb MS, Pietras RJ, Gunnar RM, et al: Paroxysmal ventricular fibrillation in two patients with hypomagnesemia—Treatment by transvenous pacing. Circulation 37:210-215, 1968

19. Zipes DP, Festoff B, Schaal SF, et al: Treatment of ventricular arrhythmias by permanent atrial pacemaker and cardiac sympathectomy. Ann Intern Med 68:591-597, 1968

20. Lopez L, Sowton E: Overdriving by pacing to suppress ventricular ectopic activity. J Electrocardiol 5:65-73, 1972

Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

Malaria in California

TO THE EDITOR: A 55-year-old married white man, a truck driver from Colton, California, was seen at the Loma Linda University Medical Center emergency room. He had a one-week history of fatigue, drowsiness, malaise, myalgias, polydipsia, evening chills, fevers and profuse diaphoresis, lasting 30 to 45 minutes. Just before coming to the emergency room, he had vomited approximately half a cup of blood. On routine blood count it was found that approximately 75 percent of his red blood cells had *Plasmodium vivax* involvement. This was confirmed on thick smears.

The patient said that he had not left the country except once in 1975, when he traveled to Tijuana, Mexico. He had made one trip to Arkansas in 1979. He could not recall any previous, similar episodes or exposure to malaria. He had not had any transfusions or injections and none of his family had had malaria. He had no other medical problems except for hypertension. He had hauled wine grapes during the summer of 1980 around the Fresno area and had slept in his truck at night. He may have been bitten by mosquitoes any number of times. He was exposed to both migrant workers and the local Punjabi Indian group in that area.

In hospital he was noted to have gross hematuria. Two duodenal ulcers were found on upper gastrointestinal studies. His hemoglobin level on admission had been 9.8 grams per dl; this dropped to 7.0 grams per dl and left upper quadrant pain developed. A computed tomographic scan of the abdomen showed areas of small splenic hematomas and infarction.

This is the first case of endemic malaria reported in the continental United States since 1974, according to the Center for Disease Control in Atlanta. It was fortuitous to find malarial forms on routine blood count because, with the lack of travel outside the United States or exposure through transfusion, the patient's history would have eliminated the suspicion of malaria and delayed the diagnosis. Standard antimalarial therapy was given and the patient made a good response.

With the mobility of western Americans well established, physicians should be suspicious of acute intermittently febrile illness even without a history of travel outside the United States.

ERIC L. STIRLING, MD
Assistant Professor, Internal Medicine
THOMAS ROWSELL, MD
Resident, Internal Medicine
Loma Linda University Medical Center
Loma Linda, California

* * *

TO THE EDITOR: A 37-day-old infant boy was seen in the Contra Costa County Emergency Room in Martinez, California, on February 26, 1981, because of a cough.

At birth the patient weighed 3.0 kg following an uneventful term pregnancy and was delivered vaginally to an 18-year-old Laotian woman (primipara). The patient's mother had imigrated to the United States the previous May, at about the same time that the patient was conceived. She could recall having several bouts of a febrile illness while living in Laos. She also had spent some time in refugee camps in Thailand and Malaysia before coming to California. There had been no illness throughout the duration of the pregnancy which had been spent in Contra Costa County.

When discharged from hospital on the third day of life, the patient was found to have a smooth, firm liver edge palpable 1.0 cm below the right costal margin. The spleen was not palpable and the rest of the physical examination showed no abnormalities. At five days of age, jaundice developed. Findings on physical examination otherwise were unchanged. The diagnosis of physiologic jaundice was made and the child treated with formula and water supplements to breast feeding. Serum total bilirubin reached a maximum of 10.3 mg per dl with a maximum direct bilirubin of 2.3 mg per dl on day seven of life. Hematocrit at this time was 47 percent. Within the next six days, jaundice resolved totally. Oral candidiasis also developed during the patient's third week of life and was treated with and

responded to administration of nystatin suspension. There had been no travel outside the country.

When seen in the emergency room, the infant weighed 3.4 kg. He was pale and very lethargic. Body temperature was 38.5°C, taken rectally. The liver edge was palpable 2 cm below the right costal margin and the spleen was enlarged to 6 cm below the left costal margin. The rest of the physical examination gave normal findings. Laboratory data included a leukocyte count of 7,900 per cu mm with 19 percent neutrophils, 11 percent band cells, 68 percent lymphocytes and 2 percent monocytes. The hemoglobin measured 7.9 grams per dl, the hemotocrit 21.9 percent, the reticulocyte count was 3.0 percent, and there were 90,000 platelets per cu mm. An estimated 2 percent to 3 percent of the red cells contained malaria parasites which were later identified as *Plasmodium vivax*. Analysis of cerebrospinal fluid and urine gave results within normal limits. Cultures of urine, cerebrospinal fluid and blood were negative.

The patient was admitted to hospital with a diagnosis of congenitally acquired *Plasmodium vivax* malaria. He was treated immediately with chloroquine phosphate, 5 mg base per kg of body weight, by gavage. The same dose was given 6 hours, 24 hours and 48 hours after admission. The patient became afebrile within 36 hours and thick and thin blood smears for malaria were negative within 48 hours. Two weeks after admission, the patient was seen in clinic and was thriving. Smears for malaria were negative and the anemia had improved.

Thick and thin smears of the mother's blood made at the time of diagnosis were negative for malaria parasites. A thin smear made at the time of delivery was reviewed and was also negative. Nevertheless, the mother was treated with both chloroquine and primaquine.

As a result of this experience and with the increasing incidence of congenital and imported cases of malaria,[1-3] we are reminded to consider the diagnosis of malaria in all Southeast Asian children with fever, especially if there is hepatosplenomegaly. We continue to study the problem of screening pregnant women who have lived in or traveled through endemic areas.

CHARLES J. BERLETTI, MD
Contra Costa County Health Services
Martinez, California

REFERENCES

1. Congenital malaria in children of refugees—Washington, Massachusetts, Kentucky. Morbidity Mortality Weekly Rep 30: 53-55, Feb 13, 1981

2. Hindi RD, Azimi PH: Congenital malaria due to *Plasmodium falciparum*. Pediatrics 66:977-979, 1980

3. Woods WG, Mills E, Ferrieri P: Neonatal malaria due to Plasmodium vivax. J Pediatr 85:669-671, Nov 1974

Still More HAFE

To the Editor: Your publication of the recent state of the art letter by Drs. Auerbach and Miller on high altitude flatus expulsion (HAFE)[1] demands applause. Certainly, the importance of the syndrome cannot be overstated. While few practitioners of the art and science of medicine will encounter high altitude pulmonary edema (HAPE), many will be forced to deal with the devastating effects of HAFE with victims loudly announcing their need for medical intervention.

Unfortunately, because of psychosocial factors which mitigate against self-designation, the reporting of incidence, frequency and severity of this disorder is entirely inadequate. The resultant medical ignorance, or perhaps even medical neglect, casts a pall over the credibility of the entire medical profession. Without an adequate data base, we in the medical community cannot even begin to explore the anatomy, physiology and appropriate therapy of HAFE. We therefore propose the establishment of an international reporting system for the collection of all data relevant to this and related disorders. The acronym SCHTOOOL seems most appropriate and easily recalled—Society (for the) Collection and Historical Tabulation of Olfactory and Otherwise malOdorous Literature.

In recognition of the pioneering work and perceptual powers of the authors of this landmark report, we urge these physicians to accept the call to become overseers of all information relevant to this vital subject. Whenever possible, a representative aliquot of the pathologic material should be collected and sent to them, and they should be encouraged to do a prospective study.

In addition, the journal must be congratulated for recognizing the importance of this paper and appropriately airing it before an eager audience. Dissertations such as this are a breath of fresh air in a wilderness of largely irrelevant medical eructations.

CHARLES R. McELROY, MD
Associate Professor of Medicine
Director, UCLA Emergency Medicine Center
Los Angeles

JEROME R. HOFFMAN, MD
Assistant Professor of Medicine
UCLA School of Medicine
Los Angeles

REFERENCE

1. Auerbach P, Miller YE: High altitude flatus expulsion (HAFE). West J Med 134:173-174, Feb 1981

Diagnosis of Human Pulmonary Dirofilariasis

TO THE EDITOR: Since the publication[1] in the February issue of the first case of human pulmonary dirofilariasis (HPD) acquired in the West, I have received several inquiries from practicing physicians regarding the clinical and laboratory diagnosis of HPD vis-a-vis other solitary pulmonary nodules, particularly malignant ones. Perhaps a public reply would be of interest to others as well.

TABLE 1.—*Laboratory Data of Patients With Pulmonary Dirofilariasis*

Test	No. Examined	Results
Eosinophilia	19	Median 5% Range 0-14%
Serologic tests for filariasis	9	IHA: 6— 3+ BF: 4— 3+ CF: 1—
Search for microfilariae in the venous blood	5	All negative
Right heart catheterization for adult worm	1	Negative
Transthoracic needle aspiration	5	3 negative 2 inflammatory cells

BF = bentonite flocculation; CF = complement fixation; IHA = indirect hemagglutination

A review of the cases of HPD published in the United States[2] shows that most laboratory procedures (Table 1) give nonspecific or noncontributory results except for transthoracic needle aspirations, which have been consistently negative for malignant cells. The antigenic stimulus of a single worm is apparently too limited to elicit a systemic response detectable by current laboratory methods.

Clinically (Table 2) the most likely candidate for HPD is a white man between the ages of 40 and 60, who resides in an area endemic for the dog heartworm, had negative findings on an x-ray study of the chest about a year ago and now has a solitary pulmonary nodule 2 cm or less in diameter, which is either asymptomatic or associated with a mild respiratory illness and may be located in any lobe of the lungs.

The association of these epidemiologic criteria with a negative needle aspirate should suggest the possibility of HPD preoperatively. At this time, however, a definitive diagnosis can be made only surgically.

FLAVIO CIFERRI, MD, MPH
Southern California Permanente Medical Group
Los Angeles

REFERENCES

1. Ciferri F: Human pulmonary dirofilariasis in the West. West J Med 134:158-162, Feb 1981
2. Ciferri F: The epidemiology of human pulmonary dirofilariasis in the United States. Presented at the 29th Annual Meeting of the American Society of Tropical Medicine and Hygiene, Atlanta, Georgia, November 4-7, 1980

TABLE 2.—*Criteria in the Differentiation of Human Pulmonary Dirofilariasis (HPD) and Malignant Solitary Pulmonary Nodules*

	HPD	Malignant*
Patient Characteristics		
Residence in USA	Southeast and Northwest	
Median age	52	Over 45
Gender affinity	Male (66%)	Male
Ethnic affinity	Caucasian (90%)	
Clinical Features		
Asymptomatic	66%	Symptoms usually present
Mild respiratory illness	34%	
Radiographic Features		
Median interval from last negative chest x-ray	1 year	
Diameter of nodule	≤2cm (75%)	≥2cm
Location in the lungs	Any lobe	Predominantly upper lobes
Serial radiographs	No change	Changes likely
Final outcome	Calcification	Death

*Adapted from Fraser RG, Paré JAP: Diagnosis of Diseases of the Chest—2nd Ed, Philadelphia, W. B. Saunders, 1978

Teaching the Pelvic Examination in an Internal Medicine Residency Program

TO THE EDITOR: Teaching pelvic examination skills has been a problem in medical education. Traditionally, knowledge of gynecological examination has been acquired via textbook assignments, audiovisual materials, lectures and plastic models. In 1978 Kretzschmar described the gynecology teaching associate program (GTA) as a new method of teaching pelvic examination skills to undergraduate students.[1] According to the GTA concept, nonphysician women function as both instructors and patients for the pelvic examination using a team-teaching approach. He found that GTA's were well accepted by students. Qualities

the GTA approach brought to the educational system included an increased sensitivity, improved teaching skills in pelvic examination instruction and effective interpersonal skills which help create a nonthreatening environment for students. In recent years other authors have documented and extended the validity of a GTA-type experience in teaching the pelvic examination to undergraduate students.[2,3] In this report the authors document the positive value of teaching pelvic examination by GTA's to internal medicine residents.

As part of each internal medicine resident's curriculum at the University of Missouri-Kansas City Affiliated Hospital Program, he or she is asked to participate in a pelvic examination instruction session taught by two GTA's. Eighteen residents have completed the instruction. The GTA's are part-time teaching consultants in the Department of Obstetrics and Gynecology at Truman Medical Center whose chairman is Robert Kretzschmar, MD.[1] The goals of the program are to review each resident's cognitive, technical and interpersonal knowledge concerning the pelvic examination. A complete pelvic examination which demonstrates both technical and interpersonal skills is carried out by two GTA's. Each resident then examines a GTA who served as a patient/instructor. The GTA offers constructive feedback about technique and gives suggestions about how to make the examination a more comfortable and productive experience for both the patient and physician.

The large majority of residents who have completed the program think instruction using this method is very worthwhile. Positive comments include the immediate feedback from the patient/instructor, and the stressing of sensitivity and nonpainful techniques by the GTA's. Overall the residents feel that the program was very well organized and that the material and skills were taught by knowledgeable teachers. Three residents who felt the program was not worthwhile did so only because they had had similar instruction during their undergraduate education. They thought the program would be very beneficial for residents who did not have a similar undergraduate experience.

No major changes were suggested by the residents except that the session be reduced to approximately 1 to 1½ hours (originally, the instruction sessions lasted 2 to 2½ hours). All responders felt that this program should be required for first-year postgraduate physicians and not repeated yearly during their three year internal medicine program. Several participants felt that videotaping their sessions and reviewing them with the GTA would be an additional valuable experience. Finally, most residents thought that teaching about pathological conditions by this teaching system would be invaluable.

The authors feel that teaching the pelvic examination by this technique produces improved technical and interpersonal skills in internal medicine residents. Because of the positive feedback from residents this program has now become an established component of our internal medicine curriculum.

STEPHEN HAMBURGER, MD
Associate Professor of Medicine
University of Missouri-Kansas City
School of Medicine
Kansas City, Missouri

DEBORAH GUTHRIE, MA
Education Coordinator
Department of Obstetrics and Gynecology
Truman Medical Center
Instructor
University of Missouri-Kansas City
School of Medicine
Kansas City, Missouri

P. GAIL SMITH
Research Assistant
Department of Obstetrics and Gynecology
University of Kansas
Medical Center
Kansas City, Kansas

KITT SHAFFER
Graduate Student
Department of Anatomy
University of Kansas
Medical Center
Kansas City, Kansas

REFERENCES

1. Kretzschmar RM: Evolution of the gynecology teaching associate: An education specialist. Am J Obstet Gynecol 132:64-67, 1978
2. Johnson GH, Brown TC, Stenchever MA, et al: Teaching pelvic examination to second-year medical students using programmed patients. Am J Obstet Gynecol 121:714-717, 1975
3. Livingstone RA, Ostrow DN: Professional patient-instructor in the teaching of the pelvic examination. Am J Obstet Gynecol 132:64-67, 1978

Ave Atque Vale

TO THE EDITOR: In the correspondence section of the February 1981 issue of the journal, page 167, there is a letter from Dr. P. Hanson, entitled "Treatment for Heat Stroke Victims," that makes reference to an earlier communication on the topic that was published in the September 1980 issue. In Dr. Hanson's reference the author of the September 1980 communication was erroneously printed as "Elliston E." I write to point out that the author should be correctly identified as Elliston Farrell, MD; his name by tragic coincidence is listed in the In Memoriam section of the same issue in which Dr. Hanson's letter appears.

Dr. Farrell was an internist who practiced in Long Beach, California, and of whom it truly could be said "he was a gentleman and a scholar."

Ave atque vale!

GEORGE X. TRIMBLE, MD
St. Mary's Hospital
Kansas City, Missouri

Refer to: Bland CS: The Halsted mastectomy: Present illness and past history. West J Med 134:549-555, Jun 1981

Special Article

The Halsted Mastectomy: Present Illness and Past History

CORDELIA SHAW BLAND, *Topanga, California*

The Halsted mastectomy put American surgeons of the late 19th century ahead of competing general practitioners at home and the preeminent German surgeons abroad. It thus served economic and nationalistic drives in the nascent specialty of surgery. Such socioemotional forces—and not scientific principles—may explain why Halsted's expansion of the mastectomy to include the pectoral muscles became lastingly institutionalized.

"I WENT TO THE hospital feeling perfectly healthy and came out grotesquely mutilated—a mental and physical wreck."

These are the words of a woman who underwent a radical mastectomy in 1971. Although such anguish is customarily masked by the smiling American version of the stiff upper lip (beautifully modeled by former first and second ladies Betty Ford and Happy Rockefeller), this woman may well voice the innermost—even if transient—feelings of millions of women subjected to a radical mastectomy since it was introduced in 1882 by American surgeon William S. Halsted of Johns Hopkins.

The Halsted operation cuts out the breast, axillary lymph nodes and chest muscles. Because loss of the muscles weakens arm function and rules out plastic surgery for a reconstructed breast, the operation is acknowledged by its proponents as well as its opponents to be the most traumatic of breast cancer treatments. Surgeon George Crile, Jr, contends that "it seems to have been designed to inflict the maximal possible deformity, disfiguration, and disability."[1] Surgeon Oliver Cope, who stopped doing radical mastectomies in 1960, observes that loss of a breast is as devastating for some women as loss of the penis is for a man.[2]

Nor has the operation's greater trauma been justified by greater cure. Before the National Cancer Institute's (NCI) initiation of the first controlled study in 1971, no comparative findings existed. Surgeon C. D. Haagensen's substantial prospective study dating from 1935 had no control group,[3] and all retrospective studies have been essentially anecdotal, small-scale counts of apples mixed with oranges.[4]

The NCI study, directed by surgeon Bernard Fisher, has shown that the Halsted operation achieves no higher cure rate than the simple mastectomy that saves the muscles and uninvolved lymph nodes.[5] Surgeon Alfred Meyer confirmed this conclusion in the first large-scale (1,686 cases) restrospective study.[6] Oncologists I. Craig Henderson and George P. Canellos, in their recent major review on breast cancer, found no single local therapy to be superior to others.[7] All these widely publicized findings have fallen on the fertile soil of women's and patients' rights, with the result that limited excision (lumpectomy) followed by primary high-dosage irradiation is now considered the major alternative to radical mastectomy. Despite this improvement in treatment options, however, the American Cancer Society

The author is an editor at the University of California, Los Angeles, School of Medicine, and a free-lance writer.

Reprint requests to: Cordelia Bland, 19864 Grandview Drive, Topanga, CA 90290.

estimated in 1979 that 25,000 women (a fourth of newly diagnosed eases) would undergo radieal masteetomy that year.[8] So this 19th eentury operation eontinues into the 1980's with rumors of its demise greatly exaggerated.

Now that the controversy over the Halsted masteetomy has been decided in its erities' favor, it is timely to examine why the operation got so firmly established that it has prevailed for nearly a eentury without real evidence of merit. (The popular explanation that medieal knowledge in Halsted's day presumed breast eaneer to be loealized is assailable. At the same meeting in 1898 where Halsted reported his operation, leading surgeon Rudolph Matas maintained that breast caneer was systemie and might spread in the blood stream and by lymphatie routes other than those in the axilla—unaffeeted by Halsted's extirpation of museles and axillary nodes.)[9] Writer Rosamond Campion suggests that the proeedure has had its long reign of error beeause surgeons emotionally believed in it "with the same sineerity that Torquemada believed he made people more religious by burning them."[10] In like vein, Crile (who earried out the limited exeision of a Campion breast tumor) notes that some surgeons exoreise disease as the clergy of the Middle Ages did the devil, "regardless of the consequenees to the person."[11] Bernard Fisher confirms that surgeons' emotionalism has largely called the shots in breast eaneer treatment and views this as "almost tragic."[4]

If surgeons' emotional faith correlated with benefit to patients, controlled studies would not be needed. Rather, as psychiatrist Leon Eisenberg warns physieians, unfounded faith in treatments is a major source of medieal error for "when good evidence is laeking, the best and most dedicated of us do wrong in the sincere convietion of being right."[12]

Some doctors, as well as some patients, believe that sexism is associated with this excessive operation done by surgeons who are nearly all men on patients who are nearly all women, and surgeon William Nolen concedes that "male ehauvinism has been partly responsible for the blind perpetuation of the radieal mastectomy."[13] It seems sexist also when surgeons whose own adherence to the radieal mastectomy is emotional eritieize women for being emotional in resisting breast amputation.

Emotionalism attended the birth of the radical mastectomy. This has been obseured because the late 19th century was an era of phenomenal progress in medical seience and Halsted himself a revered leader of that progress. Medieine, however, although elassed as a biologieal scienee, is a combination of scienee, humanism and eommerce. It does not evolve simply in a test tube, a Petri dish or "the rat," but in the matrix of history, culture and socioeeonomies. Jaeques Barzun recalls the eomment by physician-poet Oliver Wendell Holmes that "the truth is that medieine, professedly founded on observation, is as sensitive to outside influenees . . . as is the barometer to changes in atmospherie density."[14] Barzun goes on to say that medieine's external conditioning is usually ignored both in and out of the profession.

Viewing the origins of the radical masteetomy in this light, I propose that economies (in the 19th eentury surgeons' competition with general practitioners) and nationalism (in the Ameriean surgeons' rivalry with their preeminent German counterparts) were more responsible for the sueeess of the radieal mastectomy than Halsted was. He was merely the ideal medium for the message of these soeioemotional forces. Nonetheless, an analysis of the history of the operation must start with Halsted for, as Cope notes, "his remarkable charaeter and influence were a substantial reason why so mueh attention was paid to his operation,"[2] and, as Fisher suggests, surgeons have "perhaps unknowingly" been defending the eminenee of Halsted all these years rather than the merits of his operation.[4] The belief in radical masteetomy is so interwoven with faith in Halsted that desanctifying the high priest of surgery could speed the end of his operation and the trend toward less traumatie treatments.

History

William Stewart Halsted embodied the success motif of his plaee and time. He was born in 1852 to the New York City families who owned the Halsted, Haines & Company drygoods importing firm. Halsted had governesses and tutors, was sent to boarding sehool at the age of 10, and graduated from Phillips Andover Academy and Yale, where he was on the class crew and captained the varsity football team. He was crushed and embittered when passed over by the Yale undergraduate society Skull and Bones, and his roommate and lifelong friend Samuel Bushnell has suggested that his brilliant medical career reflected his urge to show his elassmates the merit Skull and Bones had slighted.[15]

Halsted distinguished himself as a medical stu-

dent at Columbia, completing an accelerated internship at Bellevue Hospital in his final year of the curriculum and receiving his MD degree in 1877. His independent means enabled him to pursue postgraduate training in Austria and Germany under such foremost medical scientists as surgeon Richard von Volkmann. Halsted called his years abroad the happiest of his life. According to Sir William Osler, he was ever after very *verdeutsched* and held that "there were only three or four good surgeons in the world and they were all German."[16] His election in later years to the German Surgical Association was the honor that gave him the most gratification, despite such laurels on his native heath as honorary degrees from Yale and Columbia and election to the National Academy of Sciences.

After returning to New York, Halsted threw himself into his work with an intensity that showed his zeal for sharing the new techniques of aseptic surgery he had mastered abroad; it might also have shown something else acquired in Germany—a Herr Professor self-image as a superman of surgery. Halsted's prestige was enhanced by the rigid distance he kept from others. This isolation guarded his deep-seated personal problem of secret, lifelong drug addiction, entailing lengthy absences for cures.[16-19] He fell victim to cocaine in 1885 while testing its effects as nerve block anesthesia and acquired the morphine habit as an antidote to cocaine, as was common in those days of legal drug use.

After Halsted's death in 1922, the secret of his drug addiction leaked out. The revelations led his champions to scale up his achievements to scale down the character cloud of addiction. Thus, although his drug problem was still being debated in medical circles as late as the 1952 Halsted centenary at Hopkins, the tone of that debate is sounded by pediatrician Edwards Park in his contribution to the festschrift: "The question whether or not Halsted recovered is an entirely academic one, for his life to the very end was one of uninterrupted glory."[20] Park even likened Halsted to Descartes and Einstein.

The dark side of Halsted's life should by no means shadow his place in the sun; but this can be accorded him as a major pioneer on the frontiers of medical history without transmuting him into an Einstein of the scalpel. Although Halsted was, by virtue of his unprecedented American version of the Herr Professor of surgery, typecast as major importer of aseptic surgery to the United States, other outstanding American surgeons, such as "father of vascular surgery" Rudolph Matas, also furthered this therapeutic breakthrough and developed other surgical advances comparable to Halsted's.[21] (Halsted introduced the rubber gloves that are the very symbol of aseptic surgery not for medical science but for romance. He commissioned the Goodrich Company to make rubber gloves to protect the hands of the head operating room nurse at Hopkins, the future Mrs. Halsted, Caroline Hampton, from contact with irritating mercuric chloride solution. Halsted himself never used surgical gloves routinely and always doffed them when things were touch and go.[18])

Halsted initiated his operation for breast cancer in New York in 1882 and briefly reported his first 13 cases in *Johns Hopkins Hospital Reports* in 1891.[22] This first study, his further report of 50 cases in the same publication in 1894,[23] and his presentation of 76 cases at the meeting of the American Surgical Association in New Orleans in 1898,[9] make up the data base for the virtually routine prescription of radical mastectomies. Halsted's 1907 report of 252 patients in *Annals of Surgery* appeared long after his operation had become the prevailing procedure.

Halsted could establish his operation so easily because the cult of the expert dominated the medical world of the late 19th century and Halsted's prestige added great weight to his impact as expert. (Psychologist Abraham Maslow termed an expert someone who avoids all the small errors as he sweeps on to the grand fallacy.) In those days, according to a 1973 article in the *New England Journal of Medicine,* "the Herr Professor of the community needed only to indicate that his personal observations led him to a particular conclusion to have that conclusion accepted."[24]

Halsted's prestige could have been just what the doctor ordered for the new specialty of surgery. It was struggling hard for its share of the 19th century American dream of unlimited growth and success—in the limiting situation of too many doctors, almost all of them general practitioners who also carried out surgical procedures. Founded in 1880, the American Surgical Association, the nation's first organization of surgeons, was dedicated to rigorous quality in operating techniques and in surgeons. It was surely also concerned, however, with the new specialty's financial prospects in times that were precarious for physicians.

An overpopulation of physicians extended from the 1860's, when there was one doctor for every

572 persons,[25] until long after the 1910 landmark *Report on Medical Education* by Abraham Flexner set in motion a process of reducing the quantity while raising the quality of the nation's medical schools. The Flexner report cited "the enormous overproduction of physicians in the last 25 years" that gave the United States a doctor to population ratio four to five times higher than that of other western nations such as Germany.[26]

The profession's conflicts could not have aided fee collection. The *regular* or allopathic physicians were regrouping after prolonged assault by the homeopaths and Thomsonians,* and by the People's Health Movement organized by Sylvester Graham, a nutritionist whose name is ingrained in the graham cracker. Medical historian Richard Shryock quotes a writer in a journal of opinion who warned that the public itself would act as umpire between the regular and challenging schools of medical practice and reach its verdict after careful perusal of the undertakers' bills.[25]

Against this background of hard times Halsted's mastectomy can be seen as filling the bill for the nascent specialty—separating the surgeons from the general practitioners by a swath only skilled surgeons could cut. Surgeon Frederick Gerrish, discussant of Halsted's report of 76 cases at the 1898 meeting of the American Surgical Association in New Orleans, stated, "We now have an operation which should be regarded as unjustifiable for the general practitioner, since it demands the anatomical knowledge, the trained mind, and the steady nerves of the expert, I had almost said of the specialist."[9] Halsted was less shy in staking the specialist's claim: "Now that surgery is specialized to such an extent, surgeons have plenty of time to drill themselves in operation. They should not cast about for easy operations—for operations that anyone can do . . . ."[9] (Halsted's preference for operations of magnitude still exists. An eminent surgeon was quoted in a 1974 magazine article as warning that progress in breast cancer surgery would recede "if you do all this crappy small stuff."[10])

The simple mastectomy could be done by a general practitioner in an hour. The radical mastectomy, according to Halsted, "including the toilet of the wound and the grafting, requires from two to four hours. . . ." The greater time required for the radical mastectomy made it more profitable. Besides the higher fee, however, the professional status offered by the more technically demanding Halsted procedure promised still greater long-term reward. Halsted was far from indifferent to the pecuniary aspects of surgery. Osler wrote that "he secured a very good income from a very few patients as his fees were enormous . . . ."[16] Thanks to his enormous fees, Halsted, as recalled by neurosurgeon Harvey Cushing, long his student, "spent his medical life avoiding patients."[19]

*Homeopaths followed the "like cures like" theory—that is, drugs that in large doses produce certain symptoms counteract them in minute doses. The Thomsonian or botanic system condemned all mineral and metallic remedies.

Lifesaving

Halsted apparently referred to his operation as lifesaving* to justify its destruction of the muscles. Thus, although he admitted that his patients complained they could no longer "dress their back hair" in the elaborate fashion of the day, he advised his colleagues that "disability, ever so great, is a matter of very little importance as compared with the life of the patient,"[23] and, "We should, perhaps, sacrifice many lives if we were to consider the disability which might result from removing a little more tissue here and there."[23] He noted, "Furthermore, these patients are old. Their average age is nearly 55 years. They are no longer very active members of society."[23] (Yet Halsted seemed to contradict his own lifesaving contention by admitting in the same report that "one might literally flay the patient's chest and side only to find a few weeks or months later one or more cancer nodules in the skin of the neck or back or abdomen.")

Still invoking lifesaving in defense of the Halsted operation, a surgeon in a 1978 symposium claimed that lesser operations catering to "feminine whims" may result in "a dead woman with a somewhat more pleasant-appearing chest wall."[27] Because it is well known that each sort of treatment for breast cancer has widely varying outcomes, governed by whether the tumor is fast-growing or slow and a host of other factors, such lifesaving claims are more of the "emotionalism" Bernard Fisher deplores.

We would expect Halsted to have had a compelling medical reason for overturning the teaching of his mentor Volkmann, who had 23 years more clinical experience than he, that the muscles should be spared in the mastectomy. Volkmann explained that "I was led to adopt this procedure because on microscopic examination I repeatedly found when I had not expected it that the fascia

*That many women have a normal life span after radical mastectomy does not alter the fact that there has never been any proof that the operation is lifesaving.

was already carcinomatous, whereas the muscle was certainly not involved"[22] (findings confirmed by pathologists today).

Halsted's first report (1891) gives this explanation for excising the muscles: "It is impossible to determine with the naked eye whether or not the disease has extended to the pectoral muscles."[22] Since Volkmann found that cancer did not extend to the muscles, a finding in which Halsted concurred, to wit, "his observations were correct, and they have been confirmed in almost every detail,"[23] it is hard to understand why Halsted sacrificed the muscles because he could not see if they were invaded. Surely the inability to see if cancer existed applied also to other tissues on the borders of the operation.

In his 1894 report, Halsted advanced this quite different reason for taking the muscles:

> The pectoralis major muscle . . . should be excised in every case of cancer of the breast because the operator is enabled thereby to remove in one piece all of the suspected tissue.
>
> The suspected tissues should be removed in one piece (1) lest the wound become infected by the division of tissue invaded by the disease, or of lymphatic vessels containing cancer cells, and (2) because seeds or pieces of cancerous tissue might equally be overlooked in a piecemeal extirpation.[23]

Why Halsted decided to remove with the "suspected" tissues the muscles he agreed with Volkmann were not cancerous can only be guessed.

What Halsted lightly referred to as "removing a little more tissue here and there" has left millions of women with weakened arms. Breast surgeon Jerome Urban states that "women mind losing their muscles more than their breast, because they can hide the loss of a breast with a falsie but they can't hide the hollow in the axilla."[10] Besides the muscles' value for a woman's strength and appearance, they have a role in physical affection. Marriage counselor Eleanor Hamilton advises: "Hugging allows you to have body contact with the pectoral (chest) muscles, one of the most receptive areas of the body. Since these muscles are involved with the sexual muscles, hugging can initiate sexual feelings."[28]

That Halsted's true goal for his operation was more modest than its being lifesaving, however, is suggested by his interest in local recurrence. He was entirely candid in maintaining that "the efficiency of an operation is measured truer in terms of local recurrence than of ultimate cure."[23] Concern with local recurrence underscores his case histories. These are typical:

> CASE 4. No local or regional recurrence. Reported dead.
>
> CASE 9. Three years and two months after operation died from internal metastases. No local recurrence.
>
> CASE 10. Died with symptoms of internal metastases in seven months. Neither local nor regional recurrence.[23]

Surgeon Rudolph Matas, Halsted's friend as well as critic, countered that "a far more important question than that of local recurrence is that which refers to the actual numbers of cures obtained."[9] Matas shot down Halsted's lifesaving claim in this eloquent exposition of the tendency of breast cancer to spread in the blood stream and by lymphatic routes other than, or in addition to, the axillary lymph nodes—a challenge to the "get it all" theory as relevant to the 1980's as to the 1890's:

> We operate on the presumption that metastatic migration has followed the widest and most direct highway (the axillary route), and that the less frequent byways of travel have not yet been utilized by the enemy. Success in avoiding intrathoracic and visceral metastases must, therefore, remain, to a large extent, an affair of chance, not of certainty that all the avenues of escape from the primary focus have been cut off . . . ." The words constantly used to qualify the operation of the day as "complete" and "radical" are anatomical misnomers which serve only to indicate evolutionary phases in the surgical technique, and are illusory if used in the sense that they root out the evil with any degree of certainty.[9]

Matas concluded that Halsted's operation "offers no more prospect of cure or chance of escape from internal metastases and secondary recurrence in the neck than that obtained by the older and less mutilating operation."

Matas's caveat on the spread of breast cancer was lost on Halsted. Halsted also apparently failed to see the import of a finding by Harvey Cushing that following a mastectomy, a patient was found to have cancer growing between the costal cartilages next to the sternum. Halsted's failure to pursue the meaning of Cushing's observation set the stage for American surgeons to overlook the critical role of the internal mammary lymph nodes in the spread of breast cancer. In 1932 the French anatomist Henri Rouvière elucidated the significance of both the internal mammary lymph nodes and the posterior mediastinal nodes. He showed that breast cancer often spreads to these nodes within the chest—far out of reach of a surgeon.[29] In 1959 the surgeon R. T. Turner-Warwick of the Middlesex Hospital also cited the

importance of the internal mammary chain as a pathway of lymphatic spread of cancer from both the lateral and medial halves of the breast.[30] Recently, Urban, Haagensen and Cope have responsibly stressed the problem of the internal mammary nodes. Clearly, it can offer patients scant help to excise diseased axillary lymph nodes when cancer has spread to the internal mammary nodes as well, and in some cases it has spread to the internal mammary nodes alone.

Halsted's case results were far from lifesaving, even for his time, when a three-year survival gauged the success of therapy. Of his 50 cases reported in 1894, none were followed for more than 3½ years; 19 patients were dead, and most of the 27 counted as alive and well were less than 18 months postoperative.[23] Of his 76 cases reported in 1898 and followed up to three years, only 31 patients were alive and well. Thirty-five had died (seven with local recurrence) within three years of the operation. One wonders what induced this serious clinical scientist to claim favorable results from such a small number of dead, dying and doomed women. Sadly, Halsted's legacy of a lifesaving myth around his operation has probably deterred generations of physicians from developing treatments that *are* lifesaving—and life-serving.

Nationalism

That Halsted's mastectomy surpassed (in "thoroughness") the Volkmann operation preferred by the top surgeons of Germany must have been deeply gratifying to American surgeons. Medicine in the 19th century United States still depended on Europe for scientific developments because American physicians had little interest in research. Shryock notes that professional prestige here was gained by "a fashionable practice, which presumably aided the sick and at the same time bore the hallmark of financial success."[25] American medicine's prolonged dependence on the mother continent bred a nationalistic rivalry with medical leaders abroad.

The flagrant nationalism of the period could not have been more boldly articulated than by prominent New Orleans physician Joseph Holt in his welcoming address to the American Surgical Association in 1898, the year the United States launched the jingoistic Spanish-American War. The expansionism boasted by Holt may be seen as a metaphor for Halsted's operation presented later at the meeting. Said Holt:

> Preserving ethnological purity as an ethical instinct in our contact with the lower races, and, therefore, race dominance, we have developed and overspread islands and continents, always in the direction of greatest possibilities, albeit, sometimes of greatest resistance . . . . On this continent we did not commingle with, but wiped out, the incorrigible Indian, and extinguished the pretensions of France and Spain.[31]

Holt quotes a Dr. F. S. Dennis that "if what Americans have accomplished be climinated from the sum total of the surgical work of the world, there is little left to other nations." Holt so deplored the tradition for young American physicians to take postgraduate training in Europe that he denied it still existed (whereas it continued until at least World War I):

> In times past this yearning for a foreign diploma as next best to a foreign title, betraying a smallness of spirit and a childish vanity almost despicable and wholly un-American, was almost the rule, but is now an exception, for even with the weakest worshipper of the glittering tinsel which adorns foreign titles and honors, the center of attraction has been shifted from abroad and localized in our home institutions, not by patriotic sentiment, but by the law of natural selection in favor of the fittest, which, not always, but in this instance, is also the best.

Surgeon Theodore Prewitt concluded his presidential address to the meeting with this paean to progress:

> Railroads, steamboats, telegraph, telephone, photograph, electric light, electric motor, with many other marvellous things, have made this century the most brilliant epoch in the world's history.
>
> We are proud to say that medicine and surgery have not been laggards in this phenomenal procession of wonderful achievements. Within the period named they have leaped from a crude empiricism to a status closely approaching exact science. Will the 20th century find them keeping abreast of the advances made in the material world? Will surgery advance with strides commensurate with those of the past 50 years?[32]

Although Prewitt's belief that medicine closely approached an exact science was unfounded, his hope that 20th century medicine would advance in step with the material world was realistic. Progress in medicine and surgery has indeed exceeded his fondest dreams in many areas—but not in cancer of the breast. It is still the chief killer of American women in the prime of life, and the Halsted operation, introduced when President McKinley led a nation of 30 million souls thrilled by the first electric light, is still done today when President Reagan heads a country of 240 million citizens blasé about trips to the moon.

Conclusion

Halsted mirrored—as well as served—American surgeons' nationalistic rivalry with German

surgeons and economic competition with general practitioners. This strange confluence of conditions favored the radical mastectomy and medical science played small part in its success.

REFERENCES

1. Crile G Jr: What Women Should Know About the Breast Cancer Controversy. New York, Macmillan Publishing Co, 1973

2. Cope O: The Breast: Its Problems—Benign and Malignant—and How to Deal with Them. Boston, Houghton Mifflin Co, 1977

3. Haagensen C: Treatment of curable carcinoma of the breast. Int J Radiation Oncology Biol Phys 2:975-980, 1977

4. Fisher B: The surgical dilemma in the primary therapy of invasive breast cancer: A critical appraisal. Curr Probl Surg 3-53, Oct 1970

5. Fisher B, Montague E, Redmond C, et al: Comparison of radical mastectomy with alternative treatments for primary breast cancer. Cancer 39:2827-2839, Jun 1977

6. Meyer AC, Smith SS, Potter M: Carcinoma of the breast. Arch Surg 113:364-367, Apr 1978

7. Henderson IC, Canellos GP: Cancer of the breast: The past decade. N Engl J Med 302:17-30, Jan 3, 1980 and 302:78-79, Jan 10, 1980

8. Randal J: News story on the June 5, 1979 NIH Consensus Development Conference. New York Daily News, Jun 6, 1979

9. Halsted WS: A clinical and histological study of certain adenocarcinomata of the breast—And a brief consideration of the supraclavicular operation and of the results of operations for cancer of the breast from 1889 to 1898 at the Johns Hopkins Hospital. Trans Am Surg Assoc 16:144-181, 1898

10. Nobile P: King cancer. Esquire 108-111 and 204-225. Jun 1974

11. Crile G Jr: Surgery: Your Choices, Your Alternatives. New York, Delacorte Press/Seymour Lawrence, 1978

12. Eisenberg L: The social imperatives of medical research. Science 198:1105-1110, Dec 16, 1977

13. Nolen WA: How doctors are unfair to women. McCall's 50-52, Aug 1973

14. Barzun J: The medical profession under fire. Harper's Magazine 257:61-68, Oct 1978

15. MacCallum W: William Stewart Halsted: Surgeon. Baltimore, Johns Hopkins Press, 1930

16. Penfield W: Halsted of Johns Hopkins: The man and his problems as described in the secret records of William Osler. JAMA 210:2214-2218, Dec 22, 1969

17. Whipple AO: Halsted's New York period. Surgery 32:443-550, Sep 1952

18. Harvey AM: Early contributions to the surgery of cancer: William S. Halsted, Hugh H. Young and John G. Clark. Hopkins Med J 135:399-417, Dec 1974

19. Holman E: Osler & Halsted, a contrast in personalities. *In* McGovern JF, Burns CR (Eds): Humanism in Medicine. Springfield, IL, Charles C Thomas, 1973

20. Park EA: A pediatrician's chance recollections of Dr Halsted. Surgery 32:443-550, Sep 1952

21. Who was Dr. Rudolph Matas? Tulanian, Mar 1968

22. Halsted WS: Operations for carcinoma of the breast. Johns Hopkins Hosp Reports 2:277-280, 1891

23. Halsted WS: The results of radical operations for the cure of carcinoma of the breast performed at the Johns Hopkins Hospital from June, 1889, to January, 1894. Johns Hopkins Hosp Reports 4:297-327, 1894

24. Weiner M: Raw vs cooked data. N Engl J Med 289:974-976, Nov 1, 1973

25. Shyrock RH: Medicine in America: Historical Essays. Baltimore, Johns Hopkins Press, 1966

26. Flexner A: Medical Education in the United States and Canada—Report to The Carnegie Foundation for the Advancement of Teaching, Bulletin No. 4, 1910. Boston, DB Updike, The Merrymount Press, 1910

27. Ariel IM: The treatment of breast cancer by radical and super radical mastectomy. Resident Staff Physician 57-62, Sep 1978

28. Sandler L: How touching can help strengthen a marriage. Nat Enq, Jun 7, 1977

29. Rouvière H: Anatomie des lymphatiques de l'homme. Paris, Masson et Cie, 1932 (Rouvière H: Anatomy of the Human Lymphatic System, translated by Tobias MJ. Ann Arbor, Michigan, Edwards Brothers, Inc, 1938)

30. Turner-Warwick RT: The lymphatics of the breast. Br J Surg 46:574-582, 1959

31. Holt J: Address of welcome. Trans Am Surg Assoc 16: c-xii, 1898

32. Prewitt TF: Address of the president. Trans Am Surg Assoc 16:1-5, 1898

Refer to: Pepitone-Rockwell F, Baker S, Moore DM, et al: Notes on health issues for women (Information). West J Med 134:556-561, Jun 1981

Notes on Health Issues for Women

Understanding the Medical and Psychological Aspects of Rape

RAPE HAS BEEN CALLED "the ultimate violation of self" and "is best understood in the context of a crime against the person and not against the hymen." In incidence, rape is the fastest rising violent crime in the United States, and physicians will be increasingly called upon to treat the victims.

As an act of violence, rape instills in its victims a perceived brush with death; concomitantly, the victims' responses are equally dire. This cluster of physical, emotional and behavorial responses has been identified as the rape trauma syndrome. This syndrome includes such major phobic reactions as fear of being indoors, fear of being outdoors, fear of being alone, fear of crowds, fear of people behind one and sexual fears. Other responses include self-blame, suicidal ideation, a sense of feeling out of control and shock. All of these responses are adaptive and are normal coping strategies.

Keeping in mind that victims tend to be either expressive or controlled in their responses to the trauma of rape, some hints for psychological support include the following.

- Encourage the victim to talk about her feelings, but only if she wants to.
- Try not to determine the validity of the rape; such a determination is made in the courtroom, not by physicians.
- Inform the victim of resources available to her such as police and legal procedures, information for victims of violent crimes, supportive community groups and medical facilities.
- Assume that because rape is a traumatic event, victims may show a wide range of emotional and behavorial responses.
- Try, with the victim's consent, to involve her family and friends in providing emotional support.

Medical intervention on the part of a physician may include assessment and treatment of physical injuries as well as completing the evidentiary examination. The victim needs to sign consent forms for both of these procedures *before* they are initiated. She has the right to request medical treatment only and to refuse the evidentiary examination. In any event, no information may be released unless the patient, parent or guardian gives authorization.

The physician is responsible for overseeing the following medical aspects of the effects of rape. (1) A brief history and interview should be obtained to ascertain the nature of the injuries. The victim should be asked if she has douched, bathed or changed clothes since the assault. (2) The clothing should be noted, described, reported and retained. (3) Trauma must be diagnosed and a gynecological examination made. The vagina and cervix should be examined and swabs obtained for a wet mount, acid phosphatase, dry and fixed smears. Oral and rectal swabs and smears may also be collected. (4) The possibility of pregnancy should be raised and treated with administration of 0.25 mg of diethylstilbestrol (DES) twice a day for five days if the victim was not already pregnant before the rape. Menstrual extraction two or six weeks following the rape should be discussed as well as the possibility of a suction abortion at the six-week checkup should pregnancy occur. (5) Baseline information for the presence of gonorrhea, syphilis and the less common venereal diseases should be obtained. Intramuscular procaine

Reprint requests to: Fran Pepitone-Rockwell, PhD, Director, Women's Resources and Research Center, TB 116, University of California, Davis, School of Medicine, Davis, CA 95616.

penicillin may be given prophylactically. Follow-up appointments at two or six weeks in the gynecology clinic should be given to assess gonococcal cultures and the VDRL. The VDRL should be repeated six weeks after the assault.

Responses to rape have been compared with those experienced after trauma by victims of war. Thus, physicians must recognize the complexity of the medical and psychological problems of victims of rape.

FRAN PEPITONE-ROCKWELL, PhD
Director, Women's Resources and Research Center
Assistant Professor
Department of Psychiatry
University of California, Davis, School of Medicine
Davis, California

REFERENCES

Bard M, Ellison K: Crisis intervention and investigation of forcible rape. Police Chief 41:68, 1974

Hilberman E: Rape: The ultimate violation of the self. Am J Psychiatry 133:436-437, Apr 1976

McCombie SL, Bassuk E, Savitz R, et al: Development of a medical center rape crisis intervention program. Am J Psychiatry 133:418-421, Apr 1976

Burgess A, Holmstrom L: Rape: Victims of Crisis. Bowie, MD, Robert J. Brady, Co., Subsidiary of Prentice-Hall Co., 1974

Hilberman E: Medical aspects of rape. *In* The Rape Victim. Washington, DC, American Psychiatric Association, 1976

Pepitone-Rockwell F: Patterns of rape and approaches to care. J Fam Pract 6:521-529, Mar 1978

Battered Wives

SINCE THE PUBLICATION of Del Martin's *Battered Wives* in 1976, wife beating has become an issue of national concern, with groups as wide-ranging as women's grassroots organizations, professional practitioners, researchers and legislators becoming involved. Unlike rape and most other forms of violence against women, wife beating occurs within the confines of a relationship which, presumably, has been built on a foundation of love and trust and which has been socially approved and legally protected. The nature of the marital relationship creates a complex set of social and psychological factors with which battered wives and their helpers must cope. Like other victims of violence, a battered wife finds herself victimized twice: first by the perpetrator and second by society through its assumptions about her and how it treats her.

The danger of dealing with battered women and those who have beaten them is that of viewing them as different from other men and women. Researchers predict that up to 50 percent of American families will experience one or more episodes of violence. It is necessary, therefore, to view this issue not merely as one related to individual persons but as one having its roots in (1) historical attitudes toward women, (2) rigid sex role socialization, (3) power relationships between men and women and (4) traditional views of the nature of marriage. Data indicate that battering occurs at virtually all levels of American society regardless of socioeconomic class, ethnicity, education, employment, geographic location or other demographic factors.

The Battering Cycle and Its Consequences

Lenore Walker has identified a three-phase cycle which helps to explain the act of battering and to build a framework within which solutions can be determined. Phase I is the tension-building stage during which the man's tension and frustration grow. Phase II involves the acute battering incident during which the beating occurs. Phase III is the loving respite stage during which the man showers the woman with apologies, love, affection and gifts and promises that the abuse will not happen again. Phase III, of course, is the one which hooks the woman into staying. While his promises are easy to believe after the initial beating, as abusive incidents continue, it becomes obvious to the woman that they will not stop. By this time, however, a phenomenon called learned helplessness frequently develops, which destroys the woman's ability to leave or seek outside help.

The construct of learned helplessness describes a process wherein uncontrollable, random, noxious experiences occur and thereby limit later problem-solving and cognitive ability, cause motivational and affective disorders and decrease the behavioral response repertoire. In the case of a battered wife, the woman has "learned" that she has no control over her environment and therefore stops making any attempts to change her circumstances. Attribution theory examines the effects of a woman's perceptions of her own responsibility for the battering as well as the relationship of those perceptions to the development of learned helplessness. Learned helplessness is the consequence of a battering relationship for the woman—without intervention it will get worse; however, with help it can be reversed as the woman begins to regain control in her life.

The Woman

Walker points out that a woman remains in the battering relationship for a variety of complex

psychosocial reasons. The battered woman experiences a number of predictable emotions: fear, guilt, embarrassment and shame, anger, helplessness, powerlessness, low self-esteem, a fear that she is insane, and feelings of isolation and ambivalence. Further, she remains in the situation for a variety of equally predictable reasons: possible economic, emotional or physical dependency; a lack of support from others for leaving; lack of anywhere to go; belief in a traditional value system which demands that she stay in her marriage at all costs, and concern for her children and husband. In addition, the woman's learned helplessness assists in creating a symbiotic relationship which leaves both the woman and the man afraid that they cannot survive alone.

The Man

Common characteristics of the abuser include extreme jealousy, belief in a traditional value system which puts him in charge of his wife and gives him the right to do with her as he wishes, heavy drinking or drug abuse, history of either child abuse or spouse abuse in his own childhood home, inability to tolerate frustration, a violent temper often triggered by minor things, cruelty to animals, preoccupation with weapons, emotional disturbance, a pattern of blaming others for his own behaviors or failures, low self-esteem especially related to his masculinity, acceptance of violence as a means of solving problems and unemployment or job dissatisfaction.

The Children

While relationships between wife abuse and child abuse are just beginning to receive attention, a few observations have already been noted: (1) men who abuse their wives also tend to abuse their children; (2) women who are abused may vent their anger and frustration on their children; (3) children frequently become accidental victims of spouse abuse and (4) children who are abused tend to grow up to be child abusers and children who witness spouse battering tend to grow up to be wife beaters or abused wives.

It appears that violence as a means of problem solving is a learned behavior and that children learn violence very well from their parents. Anyone suspecting spouse abuse needs to take it seriously for both the effects it may have on the woman and those it may have on her children.

Medical Personnel: Intervention Techniques

- Become familiar with community resources for women.
- Become aware of symptoms experienced by battered women including repeated incidents of headaches, choking sensations, hyperventilation, asthma, chest pains, gastrointestinal symptoms, pelvic pain, back pain, allergic phenomena, heart disease, epilepsy and frequent suicidal thoughts or behaviors. All stress-related symptoms should be explored carefully as should any bruises or injuries, particularly around the face, head, legs, breasts or abdomen.
- If abuse is suspected, ask the patient directly about her condition. Failure to ask may be interpreted as implicit approval of her abuse. If you suspect battering, examine and interview the patient alone so she may be provided with an atmosphere in which to discuss her situation.
- If the patient reports abuse, believe her and either help her explore available options or refer her to someone who is able to assist her.
- If a patient is referred for counseling, explain why so that she may receive help in improving her coping techniques and in overcoming her helplessness, instead of believing that she is responsible for her own victimization.
- Be cautious about prescribing tranquilizers or other drugs which may inappropriately help her to "calm down" or to tolerate an abusive situation that is both psychologically and physically dangerous to her and her children.
- Whenever possible, a woman who has just been beaten should be admitted to hospital to avoid returning her to a situation which may still be dangerous.
- Be nonjudgmental about both the patient and her husband.

DONNA M. MOORE, MA
Human Resources and Affirmative Action Officer
Montana State University
Bozeman, Montana

REFERENCES

Moore DM: Battered Women. Beverly Hills, CA, Sage Publications, 1979

Walker L: The Battered Woman. New York, Harper & Row, 1979

Gelles RJ: The Violent Home. Beverly Hills, CA, Sage Publications, 1974

Fleming JB: Stopping Wife Abuse. New York, Anchor Press, 1979

Hilberman E, Munson K: Sixty battered women. Victimology: Int J 2:460-470, Feb 1978

Stark E, Flitcraft A, Frazier W: Medicine and patriarchal violence: The social construction of a 'private event.' J Int Health Services 9:461-493, 1979

Women in Medicine: Myths and Realities

WOMEN CONSTITUTE 54 percent of the population of the United States, yet they make up only 11 percent of the physician population. In the 130 years since Elizabeth Blackwell became the first woman to graduate from a medical school in this country, little progress was made in redressing this inequity until the 1970's. Since 1970, the percentage of female students has increased from 9.6 percent to 24 percent. However, myths persist about women physicians which may inhibit the continued growth in the number of women in medicine. Some of these myths are discussed below.

Women physicians are less productive than men physicians. Studies in the 1950's and early 1960's indicated that women physicians practiced 40 percent fewer hours than men. Recent data indicate that women physicians work 90 percent of the hours practiced by their male colleagues. The time out of medicine is the equivalent of slightly less than 12 months and is accounted for almost entirely by childbearing and childrearing responsibilities. Interestingly, none of these studies took into account the fact that women physicians have a working life expectancy that exceeds that of men physicians by a year and a life expectancy that exceeds that of men physicians by five full years.

Women physicians are less satisfied with medicine than men physicians. The available data suggest that despite some restrictions in choice of speciality, women are as satisfied with their medical careers as men.

A career in medicine is "unhealthy" for women. When compared with the US female population, women physicians have a lower mortality in every age group. This is especially true for women physicians in California, for whom actual deaths are found to be 91.9 percent of expected deaths.

It is difficult for a woman to get into medical school. Women are accepted into medical school in direct proportion to the number of women applicants. In the past ten years there has been no evidence that admissions committees nationwide underselect women. There are some instances where overselection, in terms of numbers, is evident.

Women in medicine have more psychopathologic problems than men. While the data in this area are sparse they indicate that women physicians appear to require admittance to psychiatric hospitals less frequently (but for the same types of problems) than men. Being a physician and a mother was not a factor in the cause of the problems precipitating admittance to psychiatric hospital. The incidence of suicide for women physicians and women medical students is three to four times greater than that for their nonphysician peers but is almost exactly the same as for their male colleagues in medicine.

Clearly, not all barriers to being a women physician have been eliminated. Unique but very real problems remain for women who choose to practice medicine.

Women continue to experience prejudice and barriers in the choice of speciality. Women medical students report that surgery and surgical subspecialities and, in some cases, obstetrics-gynecology are the areas that reflect the greatest prejudice against their entry. Women are substantially under-represented in the surgical specialities and over-represented in pediatrics and psychiatry.

Being a physician, wife and mother is extraordinarily demanding. These demands are felt in a variety of ways. Women physicians have a 48 percent higher divorce rate than men physicians. Women physicians are considerably more likely to remain single (31 percent versus 2 percent). When they do marry, they will have fewer (2.5) children than the spouses (3.2) of their male colleagues. Also, they are more likely to marry another physician (36 percent) than their male peers (2 percent). The triple role of physician, wife and mother is extraordinarily demanding in time and energy, and women physicians feel even more *pushed* and *pulled* than do men physicians.

Patients have stereotyped views of physicians. Patients in the United States have sex-typed views of medical roles and 96 percent report that the typical physician is a man. Seventy-eight percent of patients prefer men physicians and view women physicians as less competent and less experienced. This prejudicial stereotype breaks down when the patients have had experience with a woman physician. Thus, as the number of women in medicine increases, this problem will diminish. The most negative attitudes were voiced by Span-

ish speaking patients while the most positive attitudes were expressed by black women and obstetric patients.

Myths serve to dissuade young women from choosing medicine as a career more than do the actual problems indicated above. Practical solutions exist for dealing with the latter. Sex stereotypes are slowly losing their influence as awareness of sexism increases. As more patients are treated by women physicians, patients and physicians alike will come to accept women physicians as major assets in medicine.

FRAN PEPITONE-ROCKWELL, PhD
Director, Women's Resources and Research Center
Assistant Professor
Department of Psychiatry

DON A. ROCKWELL, MD
Associate Dean, Student Affairs
Professor
Department of Psychiatry
University of California, Davis, School of Medicine
Davis, California

REFERENCES

Heins M, Smock S, Martindale L, et al: Comparison of the productivity of women and men physicians. JAMA 237:2514-2517, 1977

Goodman LJ: The longevity and mortality of American physicians, 1969-1973. Milbank Mem Fund Q 353-375, Summer, 1975

Vincent MO: Female physicians as psychiatric patients. Can Psychiatr Assoc J 21:461-465, 1976

Austin G, Maher M, Lomonaco C: Women in dentistry and medicine: Attitudinal survey of educational experience. J Dent Educ 37:11-17, 1973

Engleman EG: Attitudes toward women physicians. West J Med 120:95-100, 1974

Incest

INCEST OR intrafamilial sexual abuse involving a child and a parent or parent figure may involve as many as 2 to 3 children per 1,000 families in the United States. Intrafamilial sexual abuse of a child is the most easily concealed, least publicized and most distressful form of child abuse and may be more common than physical abuse. Most cases reported involve a female child and a male parent or parent figure.

Sexual abuse of a child by a family member often disrupts the whole family; therefore, many cases are overlooked or ignored by professionals eager to avoid such agitation. As a result many girls who do report intrafamilial sexual abuse are viewed with suspicion and sometimes even hostility. The report is often considered a lie or a fantasy. However, children do not fabricate stories of detailed sexual activities unless they have witnessed them, and every report needs to be investigated thoroughly.

In some instances a child's report of sexual abuse by a family member is verified, but the professional involved fails to intervene on her behalf because of a belief that the child is seductive and, therefore, in some way responsible for the abuse. This attitude reflects a prejudice against child victims of sexual abuse and diminishes the concept that the adult is primarily responsible for his behavior and for initiating a sexual relationship with a highly vulnerable, developmentally immature child incapable of giving informed consent to such a relationship.

Incest and other intrafamilial sexual abuse involving a child is covered by mandatory child abuse reporting laws in most states, and physicians as well as all other health care professionals are required to report known or suspected cases. Early identification and intervention on behalf of the child may prevent long-term emotional damage and help to break the intergenerational chain of intrafamilial sexual abuse.

Vital to the process of early identification and intervention is the recognition of high-risk populations as well as physical and behavioral indicators. Incest and intrafamilial sexual abuse of a child differs from rape in that (1) the sexual abuse usually takes place over years rather than in a single incident, (2) the victim is emotionally and physically dependent on the abuser and, therefore, may be ambivalent about initiating a report, and (3) there is *covert* permission given for the abuse by other family members (particularly the mother) by their lack of effective intervention on the child's behalf.

Because of the nature of intrafamilial sexual abuse there is often no clear physical evidence of the abuse. However, there are some physical indicators which should alert physicians to consider the possibility that sexual abuse may be taking place: (1) Genital injuries such as tearing, inflammation or bruising, especially when the bruises occur around the vagina or buttocks and the injury is more severe internally than externally; (2) venereal disease of the eyes, mouth, anus or genitalia of a young child; (3) evidence of semen (oral, rectal, vaginal); (4) repeated or unexplained vaginal infections; (5) genital warts when there is no believable explanation as to the cause; (6) pregnancy in young girls when the child and the family offer a reluctant or unlikely explanation of her partner; (7) pregnancy in young girls when the family refuses to acknowledge the pregnancy or to obtain proper prenatal care for the child, and

(8) parents who are substantially overprotective of their child, refusing to allow her to talk alone with medical personnel or to obtain proper medical care.

In many communities family treatment programs now exist or are being developed to provide alternatives to prosecution or incarceration following intrafamilial sexual abuse of children. These programs report a higher number of families that have been reunited successfully and a lower number of repeated incidents of child sexual abuse after completion of the treatment program. Medical personnel can play an important role in identifying victims of intrafamilial sexual child abuse and in intervening on the behalf of these children if they are willing to recognize that the problem exists.

SANDRA BAKER, MSW, LCSW
Director
Sacramento Child Sexual Abuse Program
Sacramento, California

REFERENCES

Kempe HC: Sexual abuse—Another hidden pediatric problem. Pediatrics 62:382-389, Sep 1978

Zaphiris AG: Father-daughter incest: Definitional perimeters of the relationship and its diagnostic assessment and treatment dimensions. Read before the World Mental Health Congress, Salzburg, Austria, Jul 1979

Child Abuse: The Problem of the Abused and Neglected Child (Public Information Pamphlet No. 8). Sacramento, Crime Prevention Unit, Office of the Attorney General, Department of Justice, Oct 1978, pp 1-42

Educational Material on Large Bowel Cancer

Large Bowel Cancer: Biology and Control, a new exhibit and brochure prepared by the National Large Bowel Cancer Project, is ready for distribution through the American College of Surgeons.

Divided into three topic areas, "Finding the Cause," "Current Management" and "Toward the Solution," the three-panel exhibit and 36-page brochure are particularly suited for teaching seminars, national meetings and workshops on cancer of the large bowel.

The exhibit and brochures can be obtained separately or together. There is no fee for either, except for shipping charges. For further information, please contact Ms. Irene J. Diament, Administrative Assistant, Cancer Department, American College of Surgeons, Chicago, IL 60611 (312) 664-4050.

in memoriam

California Medical Association

ANDERSON, ARTHUR M., Castro Valley. Died April 7, 1981, aged 58. Graduate of the University of Michigan Medical School, Ann Arbor, 1946. Licensed in California in 1954. Dr. Anderson was a member of the Alameda-Contra Costa Medical Association.

ANNES, GEORGE P., San Francisco. Died April 4, 1981 in Tiburon of cancer, aged 43. Graduate of the University of Texas Medical Branch, Galveston, 1960. Licensed in California in 1963. Dr. Annes was a member of the San Francisco Medical Society.

ANTIPA, AUGUST ALEXANDER, San Francisco. Died April 8, 1981 in San Francisco, aged 68. Graduate of the University of California Medical School, Berkeley-San Francisco, 1938. Dr. Antipa was a member of the San Francisco Medical Society.

BAILEY, WILBUR, Los Angeles. Died February 11, 1981, aged 76. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1930. Licensed in California in 1931. Dr. Bailey was a member of the Los Angeles County Medical Association.

BAKER, HARRY V., Napa. Died April 25, 1981 in Napa, aged 85. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1924. Licensed in California in 1924. Dr. Baker was a retired member of the Napa County Medical Society.

BAKER, WILLIAM F., San Diego. Died in November 1980, aged 52. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1956. Licensed in California in 1957. Dr. Baker was a member of the San Diego County Medical Society.

BOSCOE, CARMEN T., Oakland. Died March 29, 1981 in Oakland of myocardial infarct, aged 81. Graduate of Eclectic Medical College, Cincinnati, 1929. Licensed in California in 1934. Dr. Boscoe was a retired member of the Alameda-Contra Costa Medical Association.

CARROLL, CHARLES WALLACE, Thousand Oaks. Died February 28, 1981, aged 54. Graduate of the University of Kansas School of Medicine, Lawrence-Kansas City, 1957. Licensed in California in 1968. Dr. Carroll was a member of the Ventura County Medical Society.

ELLIOTT, JOHN MONET, San Francisco. Died March 7, 1981, aged 61. Graduate of the George Washington University School of Medicine, Washington, DC, 1946. Licensed in California in 1947. Dr. Elliott was a member of the San Francisco Medical Society.

FAGERSTROM, DUDLEY PAUL, San Jose. Died April 16, 1981 in San Jose, aged 90. Graduate of the Northwestern University Medical School, Chicago, 1920. Licensed in California in 1924. Dr. Fagerstrom was a retired member of the Santa Clara County Medical Society.

GRODNER, ALBERT S., San Diego. Died April 11, 1981 in Mission Hills, aged 44. Graduate of Boston University School of Medicine, 1961. Licensed in California in 1968. Dr. Grodner was a member of the San Diego County Medical Society.

HANSEN, DONALD J., San Diego. Died in January 1981, aged 64. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1939. Licensed in California in 1939. MD degree from California College of Medicine, 1962. Dr. Hansen was a member of the San Diego County Medical Society.

LE DUC, ISIDOR ECTOR, San Diego. Died in March 1981, aged 75. Graduate of the University of California Medical School, Berkeley-San Francisco, 1931. Licensed in California in 1931. Dr. Le Duc was a retired member of the San Diego County Medical Association.

LEET, ROBERT S., Walnut Creek. Died April 3, 1981, aged 78. Graduate of the University of Cincinnati College of Medicine, 1927. Licensed in California in 1930. Dr. Leet was a retired member of the Alameda-Contra Costa Medical Association.

LEVINE, JULIUS, Hayward. Died April 13, 1981 in Oakland of cancer, aged 66. Graduate of the University of Arkansas School of Medicine, Little Rock, 1937. Licensed in California in 1946. Dr. Levine was a member of the Alameda-Contra Costa Medical Association.

MACPHERSON, JOHN P., San Diego. Died in March 1981, aged 76. Graduate of the University of Michigan Medical School, Ann Arbor, 1931. Licensed in California in 1932. Dr. Macpherson was a retired member of the San Diego County Medical Society.

MANN, ARLENE, San Francisco. Died April 22, 1981 in San Francisco, aged 59. Graduate of the University of Nebraska College of Medicine, Omaha, 1944. Licensed in California in 1947. Dr. Mann was an associate member of the San Francisco Medical Society.

MCCULLOUGH, GWEN, Stockton. Died April 8, 1981 in Stockton of cancer, aged 69. Graduate of the New York University College of Medicine, New York, 1939. Licensed in California in 1945. Dr. McCullough was a member of the San Joaquin County Medical Society.

MCIVER, ROBERT, San Diego. Died in October 1980, aged 73. Graduate of the College of Physicians and Surgeons, Columbia University, New York, 1935. Licensed in California in 1940. Dr. McIver was a retired member of the San Diego County Medical Society.

NEFT, LOUIS G., Yucca Valley. Died March 17, 1981 in Yucca Valley of myocardial infarction, aged 52. Graduate of the University of Pittsburgh School of Medicine, 1955. Licensed in California in 1959. Dr. Neft was a retired member of the Mendocino-Lake County Medical Society.

PORTA, ROY WALTER, San Francisco. Died February 12, 1981, aged 57. Graduate of Hahnemann Medical College & Hospital of Philadelphia, 1949. Licensed in California in 1950. Dr. Porta was a member of the San Mateo County Medical Society.

PYE, ROBERT L., Woodland. Died February 11, 1981 at Stanford University Hospital, aged 65. Graduate of New York University College of Medicine, 1943. Licensed in California in 1950. Dr. Pye was a retired member of the Yolo County Medical Society.

SCHWARTZ, MERVIN H., Roseville. Died April 3, 1981 at Stanford University Medical Center, aged 56. Graduate of Temple University School of Medicine, Philadelphia, 1951. Licensed in California in 1956. Dr. Schwartz was a member of the Alameda-Contra Costa Medical Association.

TERRY, JAMES G., Pleasanton. Died October 29, 1980, aged 73. Graduate of the University of California Medical School, Berkeley-San Francisco, 1936. Licensed in California in 1936. Dr. Terry was a retired member of the Alameda-Contra Costa Medical Association.

VAN METER, RICHARD, Fresno. Died March 30, 1981, aged 52. Graduate of Washington University School of Medicine, St. Louis, 1954. Licensed in California in 1956. Dr. Van Meter was a member of the Fresno-Madera Medical Society.

WALTON, GEORGE E., Palo Alto. Died March 16, 1981, aged 97. Graduate of Oakland College of Medicine & Surgery, 1912. Licensed in California in 1912. Dr. Walton was a retired member of the Alameda-Contra Costa Medical Association.

WEISS, PAUL OSCAR, San Jose. Died March 24, 1981 in San Jose, aged 61. Graduate of the University of Bologna School of Medicine, Bologna, Italy, 1950. Licensed in California in 1960. Dr. Weiss was a retired member of the Santa Clara County Medical Society.

WICKLIFFE, J. THOMAS P., Escondido. Died March 24, 1981, aged 86. Graduate of the University of Louisville School of Medicine, 1918. Licensed in California in 1958. Dr. Wickliffe was a member of the San Diego County Medical Socicty.

ZACH, FRANK STEFAN, San Francisco. Died April 7, 1981, aged 64. Graduate of Medizinische Fakultät der Universität, Wien, 1940. Licensed in California in 1955. Dr. Zach was a member of the San Francisco Medical Society.

New Mexico Medical Society

COULSON, EUGENE LEE, Socorro. Died April 1, 1981 in Socorro, aged 57. Graduate of the University of Colorado School of Medicine, Denver, 1958. Licensed in New Mexico in 1959. Dr. Coulson was a member of the Mid-Rio Grande County Medical Society.

Utah State Medical Association

CATLIN, JAMES M., Ogden. Died March 25, 1981 in Ogden, aged 65. Graduate of Northwestern University Medical School, Chicago, 1943. Licensed in Utah in 1950. Dr. Catlin was a member of the Weber County Medical Society.

Washington State Medical Association

CUNNINGHAM, JAMES E., Spokane. Died October 24, 1980 in Spokane, aged 80. Graduate of the Creighton University School of Medicine, Omaha, 1936. Licensed in Washington in 1937. Dr. Cunningham was a retired member of the Spokane County Medical Society.

SCHWIND, FREDERICK J., Tacoma. Died March 10, 1981, aged 65. Graduate of the University of Michigan Medical School, Ann Arbor, 1943. Licensed in Washington in 1946. Dr. Schwind was a member of the Pierce County Medical Society.

SNYDER, GLEN E., Deer Park. Died February 8, 1981, aged 82. Graduate of the State University of Iowa College of Medicine, Iowa City, 1926. Licensed in Washington in 1927. Dr. Snyder was a retired member of the Spokane County Medical Society.

AUTHOR INDEX

Abele, John S., San Francisco ..... (Mar) 198
Abrahams, Lisa A., San Francisco ..... (Jun) 535
Achuff, Stephen C., Baltimore ..... (Jan) 55
Ahn, Changwoo, Fontana, CA ..... (Mar) 212
Altus, Philip, Tampa, FL ..... (May) 455
Apfelberg, David B., Palo Alto, CA ..... (Feb) 104
Auerbach, Paul, Philadelphia ..... (Feb) 173

Baker, Sandra, Sacramento, CA ..... (Jun) 560
Barnett, Richard C., Santa Rosa, CA ..... (Feb) 170
Barrett, Cynthia T., Los Angeles ..... (Jun) 506
Bashore, Richard A., Los Angeles ..... (Jun) 506
Beers, Richard, Santa Rosa, CA ..... (Feb) 170
Bennett, Robert M., Portland ... (Jan) 71, (May) 405
Benowitz, Neal L., San Francisco ..... (Jan) 65
Berletti, Charles J., Martinez, CA ..... (Jun) 545
Biakanja, Krist A., San Jose, CA ..... (Jan) 80
Bland, Cordelia Shaw, Topanga, CA ..... (Jun) 549
Boehme, William M., Kalispell, MT ..... (May) 441
Braitman, Howard E., Oxnard, CA ..... (May) 442
Brasher, Craig, Salt Lake City ..... (Mar) 193
Breitman, Gordon, Glendale, CA ..... (Feb) 167
Brody, Garry S., Downey, CA ..... (May) 453
Brooks, George F., San Francisco ..... (May) 384
Burgess, Richard, Portsmouth, VA ..... (Apr) 357
Burt, Todd B., Salt Lake City ..... (Apr) 283
Buscemi, Jon H., Aurora, CO ..... (Jan) 69
Byrd, William E., Portsmouth, VA ..... (Apr) 357

Caggiano, Vincent, Sacramento, CA ..... (Feb) 153
Callaham, Michael, Oakland, CA ..... (May) 450
Campisi, David J., Torrance, CA ..... (Jan) 27
Castle, C. Hilmon, Salt Lake City ..... (Jan) 1
Cello, John P., San Francisco ..... (Jun) 515
Chang, Albert, Berkeley, CA ..... (Feb) 181
Chappel, John N., Reno, NV ..... (Feb) 175
Choctaw, William T., Los Angeles ..... (Jan) 7
Chudwin, David S., San Francisco ..... (May) 446
Ciferri, Flavio, Los Angeles ... (Feb) 158, (Jun) 547
Conn, Eric, Davis, CA ..... (Feb) 97
Cordes, Lester G., III, Atlanta ..... (May) 384
Cosby, Richard S., Pasadena, CA ..... (Feb) 186
Cowan, Morton J., San Francisco ..... (May) 446
Crain, Lucy, San Francisco ..... (Jan) 80
Criley, J. Michael, Torrance, CA ..... (Jan) 27

Dallman, Peter R., San Francisco ..... (Jun) 496
Dart, Charles H., Jr., Oxnard, CA ..... (May) 442
Davis, E. Y., Los Altos, CA ..... (Apr) 366
Deal, Marlene M., San Francisco ..... (May) 384
Deffebach, Roy R., Redwood City, CA ..... (May) 456
Donegan, Elizabeth A., San Francisco ..... (May) 384
Douglass, John M., Los Angeles ..... (Feb) 172
Dozier, David F., Jr, Sacramento, CA ..... (Feb) 153

Engrav, Loren H., Seattle ..... (Mar) 274
Epstein, Ernst, San Mateo, CA ..... (Feb) 167

Faris, Mary Rachel, San Francisco ..... (Jun) 535
Fessel, W. Jeffrey, San Francisco ..... (Apr) 354
Fihn, Stephan D., Seattle ..... (Mar) 263
Finch, Clement A., Seattle ..... (Jun) 532
Fitzgerald, Faith T., Davis, CA ..... (May) 424, 455
Fong, Towie, San Francisco ..... (Mar) 264
Ford, Marilyn H., Salt Lake City ..... (Jan) 1
Forrest, John V., San Diego ..... (Jun) 485
Fox, E. R. W., Coeur d'Alene, ID ..... (Jan) 73
Fremont, Albert C., San Jose, CA ..... (Jan) 80
Friedman, Paul J., San Diego ..... (Jun) 485

Garewal, Harinder S., Portland ..... (Jan) 71
Geehr, Edward, Los Angeles ..... (May) 449
Geffner, Mitchell E., Los Angeles ..... (Jan) 7
Gilkey, Fredrick, Los Angeles ..... (Jan) 27
Glassy, Frank J., Sacramento, CA ..... (Feb) 153
Gordon, Robert, Fontana, CA ..... (Mar) 212
Goyan, Jere, San Francisco ..... (May) 463
Greenspan, Francis S., San Francisco ..... (Mar) 198
Gregory, Peter B., Stanford, CA ..... (Jan) 11
Guthrie, Deborah, Kansas City, KS ..... (Jun) 547

Hale, DeVon C, Idaho Falls, ID ..... (Jun) 477
Hamburger, Stephen, Kansas City, MO ..... (Jun) 547
Hanson, Peter G., Madison, WI ..... (Feb) 167
Harbury, Christina B., Stanford, CA ..... (Feb) 128
Harker, Laurence A., Seattle .....
(Feb) 109, (Mar) 234, (Apr) 315, (May) 455
Harlan, John M., Seattle ..... (Mar) 234, (Apr) 325
Harris, Marcia, Berkeley, CA ..... (Feb) 181
Heaney, Robert P., Omaha ..... (Jan) 74
Heimbach, David M., Seattle .. (Mar) 274, (May) 454
Hepner, Gershon W., Torrance, CA ..... (May) 390
Herbert, David A., Los Angeles ..... (Apr) 354
Hess, David S., San Francisco ..... (Apr) 333
Hickman, Jack W., Tampa, FL ..... (May) 455
Hill, J. Donald, San Francisco ..... (Jun) 491
Hoefs, John C., Los Angeles ..... (May) 414
Hoffman, Jerome R., Los Angeles .....
(Jan) 60, (May) 451, (Jun) 546
Holbrook, John H., Salt Lake City ..... (Apr) 353
Hollister, Leo E., Palo Alto, CA ..... (Mar) 259
Horn, Bernard, El Cerrito, CA ..... (Jan) 72
Huebsch, Lothar B., Seattle ..... (Feb) 109
Hunt, Robert E., Portsmouth, VA ..... (Apr) 357

Iber, Frank L., Baltimore ..... (May) 438

Jacobson, Lester B., San Francisco ..... (Jun) 539
Johnson, Alan C., San Francisco ..... (May) 446
Johnson, Lloyd P., Seattle ..... (May) 379
Jordan, Alice, Berkeley, CA ..... (Feb) 181

Kahn, Arthur M., Culver City, CA ..... (May) 215
Kelso, George, Berkeley, CA ..... (Feb) 181
Kenney, John M., Santa Rosa, CA ..... (Mar) 265
Ketchum, James S., Los Angeles ..... (Jun) 506
Kishpaugh, Karla K., Salt Lake City ..... (Jan) 1
Kizer, Kenneth W., Novato, CA ..... (May) 449
Knauer, C. Michael, Stanford, CA ..... (Jan) 11
Knochel, James P., Dallas ..... (Jan) 56, (Apr) 366
Kornfeld, Howard, Berkeley, CA ..... (Apr) 365
Krebber, Hans J., San Francisco ..... (Jun) 491
Krishnamurthy, Gerbail T., Portland ..... (Mar) 220
Kudrow, Lee, Encino, CA ..... (May) 454
Kurnick, John E., Irvine, CA ..... (May) 441
Kutz, Kathleen, San Francisco ..... (Jan) 65

Lang, Howard L., San Rafael, CA .....(Mar) 265
Larlarb, Somboon, Oxnard, CA .....(May) 442
Larson, Eric B., Seattle .....(Mar) 263
Lash, Harvey, Palo Alto, CA .....(Feb) 104
Laub, Donald R., Palo Alto, CA .....(Feb) 104
Lawrence, Ruth, Davis, CA .....(Feb) 97
Lechago, Juan, Torrance, CA .....(May) 390
Lee, Stephen, Los Angeles .....(Feb) 168
Lewis, Jerry P., Davis, CA .....(Feb) 97
Lindsay, Karen L., Los Angeles .....(May) 414

Mahal, Anmol S., Stanford, CA .....(Jan) 11
Mahley, Robert W., San Francisco .....(Jan) 34
Maldowney, Bart, Palo Alto, CA .....(Feb) 104
Margoles, Michael S., San Jose, CA .....(May) 452
Maron, David J., Beverly Hills, CA .....(Apr) 367
Marvin, Janet A., Seattle .....(Mar) 274
Maser, Morton R., Palo Alto, CA .....(Feb) 104
Maun, Richard A., Whittier, CA .....(Apr) 364
Mayo, Mary, San Marino, CA .....(Feb) 186
McCrady-Kahn, Virginia L., Culver City, CA (Mar) 215
McElroy, Charles R., Los Angeles .....
(Jan) 27, 60, May) 451, (Jun) 546
Melanephy, M. Claire, San Francisco .....(May) 384
Mellor, Norman H., Corona, CA .....(Mar) 264
Meyer, Roy, San Francisco .....(Jun) 539
Miller, Theodore R., San Francisco .....(Mar) 198
Miller, York E., Denver .....(Feb) 173
Minkowski, William L., Los Angeles .....(Mar) 267
Mirea, Adrian, San Marino, CA .....(Feb) 186
Mitchell, Shiela C., Princeton, NJ .....(Apr) 348
Moore, Donna M., Bozeman, MT .....(Jun) 557
Moorefield, James M., Sacramento, CA ....(Mar) 264
Morris, R. Curtis, Jr., San Francisco .....(Jan) 56
Moses, Frank M., Aurora, CO .....(Jan) 69
Moss, Arthur J., Los Angeles .....(Apr) 296
Moss, Arthur J., Rochester, NY .....(Mar) 261
Moss, C. Wayne, Atlanta .....(May) 384
Murray, Brian J., San Diego .....(Feb) 162

Nanji, Amin A., Vancouver, BC .....(May) 452
Nelson, James A., Salt Lake City .....(Apr) 283
Newton, George W., Davis, CA .....(Feb) 97
Nielsen, Surl L., Sacramento, CA .....(Feb) 153
Nimtz, John, Santa Rosa, CA .....(Feb) 170

Oster, Henry A., Ventura, CA .....(May) 394

Palmer, Edward, Lake Oswego, OR .....(Feb) 174
Pepitone-Rockwell, Fran, Davis, CA ...(Jun) 556, 559
Peter, James B., Los Angeles .....(Apr) 365
Peters, Kenneth S., San Francisco .....(Jan) 65
Peterson, James A., Los Angeles .....(Feb) 186
Petrilli, Edmund S., Washington, DC .....(Jan) 77
Pierce, Barbara J., Idaho Falls, ID .....(Jun) 477
Piken, Edward, Torrance, CA .....(May) 390
Pointer, James, Santa Rosa, CA .....(Feb) 170
Pons, Vincent G., San Francisco .....(May) 384
Powars, Darleen R., Los Angeles .....(Jan) 7

Rapaport, Marvin, Los Angeles .....(Apr) 364
Reading, James C., Salt Lake City .....(Jan) 1
Reynolds, Telfer B., Los Angeles .....(May) 414
Rockwell, Don W., Davis, CA .....(Jun) 559
Roizen, Nancy, Oakland, CA .....(Jan) 80
Rosenbaum, David, Los Angeles .....(Feb) 168
Rowsell, Thomas, Loma Linda, CA .....(Jun) 545

Sack, Robert L., Portland .....(Mar) 223
Salz, James J., Los Angeles .....(Apr) 290
Sanmarco, Miguel E., Los Angeles .....(May) 414
Sargent, Ed, Corvallis, OR .....(Feb) 168, (Apr) 364
Sasahara, Arthur A., Boston .....(Feb) 128
Schmidt, Carlos A., Fontana, CA .....(Mar) 212
Schmidt, Eric S., Davis, CA .....(Feb) 97
Schrier, Stanley L., Stanford, CA .....(Feb) 128
Shaffer, J. Ordie, Hayward, CA .....(Apr) 361
Shaffer, Kitt, Kansas City, KS .....(Jun) 547
Sharlip, Ira D., San Francisco .....(Mar) 206
Sherry, Sol, Philadelphia .....(Feb) 149
Shore, James H., Portland .....(Mar) 223
Sickles, Edward A., San Francisco .....(Mar) 273
Siegel, Robert C., San Mateo, CA .....(Apr) 352
Siegler, Richard L., Salt Lake City .....(Mar) 193
Simon, Roger P., San Francisco .....(Jan) 87
Skeen, William F., San Francisco .....(Jun) 535
Smith, P. Gail, Kansas City, KS .....(Jun) 547
Specht, Elmer E., Portland .....(Jan) 75
Spital, Samuel E., San Diego .....(Feb) 169
Staisch, Klaus J., Los Angeles .....(Jun) 506
Stirling, Eric L., Loma Linda, CA .....(Jun) 545
Stotter, Mary Linda, Indianapolis .....(May) 450
Szarnicki, Robert J., San Francisco .....(Jun) 491

Tanner, Martha H., Idaho Falls, ID .....(Jun) 477
Taylor, Roy A., Seattle .....(May) 379
Thompson, Arthur R., Seattle ..(Mar) 234, (Apr) 315
Thorburn, Kim Marie, San Francisco .....(May) 457
Tierney, Lawrence M., Jr., San Francisco ...(Mar) 242
Tong, Theodore G., San Francisco .....(Jan) 65
Trimble, George X., Kansas City, MO .....(Jun) 548
Triplett, Willis C., Indianapolis .....(Apr) 366

Uhlmann, Richard F., Portland .....(Jan) 71

Vyas, Kokila, Portland .....(Mar) 220

Wall, Robert T., Stanford, CA .....(Feb) 128
Wallace, Helen M., Berkeley, CA .....(Jan) 80
Wara, Diane W., San Francisco .....(May) 446
White, James G., Minneapolis .....(Feb) 148
Wofsy, David, San Francisco .....(Feb) 134

Zimmermann, Emery G., Los Angeles .....(Jun) 506

IN MEMORIAM

California Medical Association:

Albrecht, John George, Jan 21, 1981 .....(Apr) 376
Allen, Orah Knapp, Nov 22, 1980 .....(Jan) 96
Amsel, Maxwell R., Nov 13, 1980 .....(Feb) 191
Anderson, Arthur M., Apr 7, 1981 .....(Jun) 562
Annes, George P., Apr 4, 1981 .....(Jun) 562
Antipa, August Alexander, Apr 8, 1981 ....(Jun) 562
Askew, Julius, Sep 27, 1979 .....(Mar) 281
Bailey, Wilbur, Feb 11, 1981 .....(Jun) 562
Baker, Harry V., Apr 25, 1981 .....(Jun) 562
Baker, William F., Nov 1980 .....(Jun) 562
Beare, William Keller, Feb 2, 1981 .....(Apr) 376
Beckner, George L., Nov 25, 1980 .....(Mar) 281
Bell, H. Glenn, Jan 28, 1981 .....(Apr) 376
Berger, Adolphus A., Nov 8, 1980 .....(Jan) 96
Boscoe, Carmen T., Mar 29, 1981 .....(Jun) 562

Bostwick, Jack R., Jr., Sep 11, 1980 ..... (Feb) 191
Bronstein, Ivan, Nov 19, 1980 ..... (Feb) 191
Burks, Arthur Lynn, Oct 30, 1980 ..... (Jan) 96
Byrne, Ralph V., Jan 19, 1981 ..... (May) 476
Carroll, Charles Wallace, Feb 28, 1981 ..... (Jun) 562
Carswell, John H., Dec 8, 1980 ..... (Feb) 191
Chapman, Paul J., Sep 13, 1980 ..... (Feb) 191
Childrey, John H., Nov 6, 1980 ..... (Feb) 191
Cloyd, David Hampton, Nov 1, 1980 ..... (Jan) 96
Cohen, Eli B., Nov 23, 1979 ..... (Mar) 281
Coke, W. Howard, Sep 4, 1980 ..... (Mar) 281
Colbert, John J., Dec 31, 1980 ..... (Mar) 281
Craton, Jean, Dec 7, 1980 ..... (Feb) 191
Dorman, George E., Sep 9, 1980 ..... (Jan) 96
Driscoll, John A., Dec 21, 1980 ..... (Mar) 281
Dunklee, George Kinney, Feb 5, 1981 ..... (May) 476
Eckardt, David L., Feb 5, 1981 ..... (Apr) 376
Edwards, Robert W., Jan 18, 1981 ..... (Mar) 281
Einhorn, Benjamin, Aug 12, 1980 ..... (Feb) 191
Elliott, John Monet, Mar 7, 1981 ..... (Jun) 562
Emerson, Philip E., Dec 30, 1980 ..... (Mar) 281
Fagerstrom, Dudley Paul, Apr 16, 1981 ..... (Jun) 562
Farrell, Elliston, Oct 26, 1980 ..... (Feb) 191
Feist, John P., Nov 8, 1980 ..... (Jan) 96
Flamson, Richard, Jan 7, 1981 ..... (Mar) 281
Footer, Wilson, Dec 12, 1980 ..... (Feb) 191
Fox, Ernest A., Nov 16, 1980 ..... (Feb) 191
Frost, Arthur J., Dec 6, 1980 ..... (May) 476
Gelfand, Ben, Jun 26, 1980 ..... (Feb) 191
Gilbert, Jack C. ..... (Apr) 376
Gibbs, William M., Sep 28, 1980 ..... (Jan) 96
Glassman, Samuel C., Oct 7, 1980 ..... (May) 476
Glyer, C. Hartley, Feb 9, 1981 ..... (Apr) 376
Goodwin, Marvin H., Jul 19, 1979 ..... (Feb) 191
Grant, Reuben S., Nov 21, 1980 ..... (May) 476
Grodner, Albert S., Apr 11, 1981 ..... (Jun) 562
Hansen, Donald J., Jan 1981 ..... (Jun) 562
Hemingway, Thomas F., Jan 18, 1981 ..... (Apr) 376
Hoagland, Paul I., Jan 29, 1981 ..... (Apr) 376
Hosford, George Newton, Jan 20, 1981 ..... (Mar) 281
Huff, George D., Jan 12, 1981 ..... (Mar) 281
Ivens, Milton Herbert, Dec 23, 1980 ..... (Mar) 281
Jackson, Robert H., Dec 18, 1980 ..... (Mar) 281
Johnson, Oscar F., Jan 16, 1981 ..... (Apr) 376
Johnston, Russell Conrad, Feb 3, 1981 ..... (Apr) 376
Jones, Glen E., Jan 25, 1981 ..... (May) 476
Kemp, George L., Nov 16, 1980 ..... (Apr) 376
Kloss, Richard G., Dec 30, 1980 ..... (Apr) 376
Kroger, William P., Jan 31, 1981 ..... (May) 476
Kwan, Sun Tao, Nov 8, 1980 ..... (Jan) 96
Landis, Raymond A., Sep 1980 ..... (May) 476
Lange, Harry W., Dec 18, 1980 ..... (Feb) 191
Lawry, Edwin V., Feb 8, 1981 ..... (Apr) 376
LeDuc, Isidor Ector, Mar 1981 ..... (Jun) 562
Leet, Robert S., Apr 3, 1981 ..... (Jun) 562
Levine, Julius, Apr 13, 1981 ..... (Jun) 562
Lowe, Frank A., Feb 7, 1981 ..... (Apr) 376
Macpherson, John P., Mar 1981 ..... (Jun) 562
Mann, Arlene, Apr 22, 1981 ..... (Jun) 562
Manning, Thomas P., Jan 18, 1980 ..... (Feb) 191
Mark, Arthur E., Apr 20, 1980 ..... (Feb) 191
Mathews, Samuel S., Sep 1980 ..... (Mar) 281
McCandliss, Robert J., Dec 5, 1980 ..... (Feb) 192
McClure, James H., Aug 23, 1980 ..... (Mar) 281
McCullough, Gwen, Apr 8, 1981 ..... (Jun) 562
McEwen, William L., Jun 1980 ..... (Feb) 191
McIver, Robert, Oct 1980 ..... (Jun) 562
McKee, Wayne P., Dec 24, 1980 ..... (Mar) 281
Merryman, George H., Jan 18, 1981 ..... (Apr) 376
Moore, Ferrall Harman, Jan 17, 1981 ..... (Mar) 281
Moore, La Rue, Oct 29, 1980 ..... (Jan) 96
Mott, John M., Nov 11, 1980 ..... (Jan) 96
Neft, Louis G., Mar 17, 1981 ..... (Jun) 563
Nelson, Donald R., Oct 26, 1980 ..... (Jan) 96
Nerad, Anton H., Dec 19, 1980 ..... (May) 476
Oier, George W., Dec 28, 1980 ..... (Apr) 376
Papadopoulos, George, Oct 23, 1980 ..... (Jan) 96
Parisi, Peter J., Dec 29, 1980 ..... (Mar) 282
Parker, James T., Jan 10, 1981 ..... (Mar) 282
Paster, Robert H., Jan 8, 1981 ..... (Mar) 282
Patterson, J. Kenneth, Nov 19, 1980 ..... (Feb) 192
Perkins, William A., Nov 10, 1980 ..... (Jan) 96
Pinto, Peter Samuel, Dec 16, 1980 ..... (Feb) 192
Porta, Roy Walter, Feb 12, 1981 ..... (Jun) 563
Pratt, Benjamin H., Jan 18, 1981 ..... (Apr) 376
Pratt, Orlyn B., Sep 25, 1980 ..... (Feb) 192
Puttler, Oliver L., Jun 14, 1980 ..... (Feb) 192
Pye, Robert L., Feb 11, 1981 ..... (Jun) 563
Robertson, Elliott, Aug 16, 1980 ..... (Feb) 192
Robuck, James C., Dec 9, 1980 ..... (Feb) 192
Rosenberger, Maurice D., Oct 13, 1980 ..... (Mar) 282
Schlueter, Francis Edward, Jan 5, 1981 ..... (May) 476
Schwartz, Mervin H., Apr 3, 1981 ..... (Jun) 563
Sloan, Julius, Nov 6, 1980 ..... (Feb) 192
Stein, David Herbert, Aug 21, 1980 ..... (Jan) 96
Stephens, Margaret A., Dec 18, 1980 ..... (Feb) 192
Stillman, Freeman L., Sep 7, 1980 ..... (Feb) 192
Strahan, Lolen Robert, Feb 6, 1981 ..... (May) 476
Struble, Homer P., Jan 4, 1981 ..... (Apr) 377
Sturr, Robert P., Jr., Jul 4, 1980 ..... (Apr) 377
Tedford, John A., Jun 7, 1980 ..... (Apr) 377
Terry, James G., Oct 29, 1980 ..... (Jun) 563
Teviotdale, James R., Dec 2, 1979 ..... (Apr) 377
Tucker, Jack S., Jan 4, 1981 ..... (Apr) 377
Twiss, Arthur Raymond, Jan 12, 1981 ..... (Mar) 282
Van Meter, Richard, Mar 30, 1981 ..... (Jun) 563
Vincent, Arthur J., Jun 5, 1980 ..... (Mar) 282
Vinetz, Joseph C., Nov 11, 1980 ..... (Feb) 192
Vinnecour, Max L., Jan 1981 ..... (May) 476
Vollmer, Henry, Feb 2, 1981 ..... (Apr) 377
Von Der Groeben, Jobst, Feb 7, 1981 ..... (Apr) 377
Waldo, Harvey Harmon, Jul 15, 1980 ..... (Mar) 282
Walton, George E., Mar 16, 1981 ..... (Jun) 563
Weiland, Albert S., Apr 28, 1980 ..... (Mar) 282
Weinstein, Morton H., Feb 4, 1981 ..... (Apr) 377
Weiss, Paul Oscar, Mar 24, 1981 ..... (Jun) 563
Wickliffe, J. Thomas P., Mar 24, 1981 ..... (Jun) 563
Wilson, David Cole, Oct 30, 1980 ..... (Jan) 96
Wong, Michael W., Dec 9, 1980 ..... (Feb) 192
Woodhull, Clayton G., Dec 16, 1980 ..... (May) 476
Yuskis, Anton S., Nov 18, 1980 ..... (Feb) 192
Zach, Frank Stefan, Apr 7, 1981 ..... (Jun) 563

New Mexico Medical Society:

Coulson, Eugene Lee, Apr 1, 1981 ..... (Jun) 563
Holle, Larry A., Mar 3, 1981 ..... (May) 476
Seibert, Virgil Everet, Jan 29, 1981 ..... (May) 476
Wells, Emery L., Mar 19, 1981 ..... (May) 476

Utah State Medical Association:

Catlin, James M., Mar 25, 1981 ..... (Jun) 563
De Mars, Harold Victor, Nov 3, 1980 ..... (Feb) 192
Farr, Keith Frederick, Dec 16, 1980 ..... (Feb) 192
Horton, Walter Harold, Feb 6, 1981 ..... (May) 476
Lippincott, Stuart W., Jan 19, 1981 ..... (May) 476
Ream, Winston Dale, Dec 27, 1980 ..... (Mar) 282

Washington State Medical Association:
Brown, William C., 1980 ..... (Mar) 282
Clarke, Donald E., Oct 9, 1980 ..... (Jan) 96
Coleman, Julian H., Feb 16, 1981 ..... (Apr) 377
Cunningham, James E., Oct 24, 1981 ..... (Jun) 563
Freeman, George W., Sep 20, 1980 ..... (Jan) 96
Goodhope, C. Richard, Nov 30, 1980 ..... (Mar) 282
Henry, Robert T., Oct 30, 1980 ..... (Mar) 282
Hofer, Amos C., Feb 7, 1981 ..... (Apr) 377
Kelly, William J., Seattle, Dec 8, 1980 ..... (Mar) 282
Luke, Henry S., Dec 11, 1980 ..... (Mar) 282
McCartney, Roy C., Dec 10, 1980 ..... (Mar) 282
McVay, John P., Dec 25, 1980 ..... (Apr) 377
Meagher, Angus C., Dec 12, 1980 ..... (Mar) 282
Parker, Dean, Jan 12, 1981 ..... (Apr) 377
Peterson, Everett R., Oct 18, 1980 ..... (Jan) 96
Schwind, Frederick J., Mar 10, 1981 ..... (Jun) 563
Smith, David W., Jan 23, 1981 ..... (Apr) 377
Snyder, Glen E., Feb 8, 1981 ..... (Jun) 563
Woolery, James W., Oct 11, 1980 ..... (Jan) 96

SUBJECT INDEX

A

Abnormal Aminopyrine Metabolism in Patients With Chronic Hepatitis, Gershon W. Hepner, Edward Piken, Juan Lechago ..... (May) 390
Accidental Hypothermia: Hypoglycemia or Hyperglycemia (Correspondence), Philip Altus, Jack W. Hickman ..... (May) 455
Reply, Faith T. Fitzgerald ..... (May) 455
Acquired Methemoglobinemia: A Resurgent Problem, Mitchell E. Geffner, Darleen R. Powars, William T. Choctaw .. (Jan) 7
Adenoidectomy, see *Tonsillectomy*
Addiction and Pregnancy, see *Heroin*
Adolescents, see *Blood Pressure in*
Advances in Burn Care (Information), David M. Heimbach, Loren H. Engrav, Janet A. Marvin ..... (Mar) 274
Correction: Use of Steroids in Burn Care, David M. Heimbach ..... (May) 454
Africa, West, see *American Physician in Rural*
Aging Heart, The—Observations in Patients 40 Years Old and Older (Information), Richard S. Cosby, Mary Mayo, Adrian Mirea, James A. Peterson ..... (Feb) 186
[Alcoholics], see *Hypophosphatemia*
[Alcoholism], see *Physician Attitudes*
Alkalinization Therapy for Tricyclic Antidepressant Overdose (Correspondence):
Mary Linda Stotter ..... (May) 450
Michael Callaham ..... (May) 450
Reply, Jerome R. Hoffman, Charles R. McElroy ..... (May) 451
American Physician in Rural West Africa (Medicine in Perspective), William L. Minkowski ... (Mar) 267
Aminopyrine in Chronic Hepatitis, see *Abnormal*
Amygdalin [Laetrile] Toxicity Studies in Rats Predict Chronic Cyanide Poisoning in Man, George W. Newton, Eric S. Schmidt, Jerry P. Lewis, Eric Conn, Ruth Lawrence (Feb) 97
[Ankylosing Spondylitis], see *Seronegative Spondylarthritis*, and *Therapy for*
Antiarrhythmic Drugs, see *Newer*
Anticoagulants, see *Thrombosis—Part II* under *Specialty Conferences*
Antidepressant Overdose, see *Alkalinization Therapy and Bicarbonate Therapy*
Antidiuretic Hormone, see *Hypokalemia*
Aorta, see *Gunshot Penetrating*
Aortoenteric Fistula [Gastrointestinal Bleeding] (Medical Staff Conference) ..... (Mar) 242
Appropriateness Review: An Overview (Correspondence), Howard L. Lang ..... (Mar) 265
Correspondence, Roy R. Deffebach ..... (May) 456
Arrhythmic Drugs, see *Newer Anti-*
Arteriosclerotic Disease, see *Platelet Connection*
Arthritis, see *Seronegative Spondyl-*
Arteritis, Giant Cell, see *Pericardial Effusion*

Articles to Read in Other Journals ..... (Mar) 280

[Asbestos Exposure], see *Mesothelioma*
Ascites, see *Unilateral Hydrothorax*
Ascites (USC School of Medicine and Rancho Los Amigos Hospital, Downey), see *Specialty Conferences*
Ascorbic Acid [Vitamin C Serum Levels] and Nutrition (Correspondence), Michael S. Margoles ..... (May) 452
Atherosclerosis, see *Role of Dietary Fat*
Atrial . . . Pacing, see *Control of Refractory*
Autoerythrocyte Sensitization, William M. Boehme, John E. Kurnick ... (May) 441
Ave Atque Vale (Correspondence), George X. Trimble ..... (Jun) 548

B

Barotrauma, see *Gastrointestinal*
[Battered Wives], see *Notes on Health Issues*
Bicarbonate Therapy for Dysrhythmia and Hypotension in Tricyclic Antidepressant Overdose, Jerome R. Hoffman, Charles R. McElroy .(Jan) 60
Correspondence,
Mary Linda Stotter ..... (May) 450
Michael Callaham ..... (May) 450
Reply, Jerome R. Hoffman, Charles R. McElroy ..... (May) 451
Biliary Duct Trauma, see *Extrahepatic*
Biopsy, see *Fine-Needle*
Bleeding After Liver Biopsy, Anmol S. Mahal, C. Michael Knauer, Peter B. Gregory .... (Jan) 11
[Bleeding], see *Disorders of Platelet Function*
[Bleeding, Gastrointestinal], see *Aortoenteric Fistula*
Blood Pressure in Infants, Children and Adolescents (Medical Progress), Arthur J. Moss ..... (Apr) 296
Editorial, Shiela C. Mitchell ..... (Apr) 348
Bone, Loss of and Fracture, see *Protection*

Book Reviews:

Annual Review of Neuroscience—Vol III, *Cowan et al* ..... (May) 474
Antimicrobial Prescribing, *Neu* ..... (Jan) 94
Computers for the Physician's Office—Vol II in the Medical Computing Series, *Zimmerman & Rector* ..... (Jan) 95
Correlative Neuroanatomy & Functional Neurology —17th Ed., *Chusid* ..... (Feb) 190
Courage to Fail, The—A Social View of Organ Transplants and Dialysis—2nd Ed., Revised, *Fox & Swazey* ..... (May) 473

Drug Interactions, 4th Ed., *Hansten* ....(Jan) 94
Fundamentals of Abdominal Sonography, *Raymond* ....(Feb) 190
Handbook of Obstetrics & Gynecology—7th Ed., *Benson* ....(May) 474
Human Patient, *Remen* ....(May) 472
Metabolic Management of the Critically Ill, *Wilmore* ....(Jan) 94
MGH Textbook of Emergency Medicine, *Wilkins et al* ....(Jan) 92
Practical Rheumatology: Diagnosis and Management, *Bluestone* ....(May) 474
Respiratory Function of the Lung and Its Control, *Grodins & Yamashiro* ....(Jan) 92
Respiratory Physiology—The Essentials—2nd Ed., *West* ....(May) 472
Textbook of Geriatric Medicine and Gerontology—2nd Ed., *Brocklehurst* ....(Jan) 93
Thyroid Cancer, *Greenfield* ....(Jan) 93
To Make the Patient Ready for Anesthesia: Medical Care of the Surgical Patient, *Vandam* ...(May) 475

Breast Reconstruction for Premalignant and Malignant Disease—An Update, David B. Apfelberg, Bart Maldowney, Donald R. Laub, Morton R. Maser, Harvey Lash ....(Feb) 104
Bronchogenic Cyst Presenting Subsequent to Intrapleural Rupture, Carlos A. Schmidt, Robert Gordon, Changwoo Ahn ....(Mar) 212
Burn Care, see *Advances in*
[Burn Wounds], see *Acquired Methemoglobinemia*
Burns, see *Lightning*

C

[Cancer], see *Breast Reconstruction*
Cancer, Lung, see *Radiologic Errors*
Carcinoma, Nasopharyngeal, see *Obstructive Sleep Apnea*
Cardiovascular Events, see *Thrombosis* under *Specialty Conferences*
Carecr Selection, see *Obstetrics and*
Cataract Operations, see *Recent Advances*
Changing Cigarette, The (Editorial), John H. Holbrook ....(Apr) 353
Children, see *Blood Pressure*
Children, see *Medical and Health Care*
Children in Day-care Centers, see *Care of Mildly Ill*
Cholesterol, see *Role of Dietary Fat*
Cigarette, see *Changing*
Clinical Medicine, Important Advances in, see *Epitomes*
Clinicopathologic Conference From UCLA: Jaundice, Hepatosplenomegaly and Liver Failure in a 60-Year-Old Woman, Discussants: David J. Campisi, Charles R. McElroy, J. Michael Criley, Fredrick Gilkey ....(Jan) 27
Colon, see *Diverticular Disease*
Control of Refractory Ventricular Ectopy by Atrial and Ventricular Overdrive Pacing, Roy Meyer, Lester B. Jacobson ....(Jun) 539
Coronary Artery System, see *Preoperative Management*
Coronary Bypass Operations (Correspondence), Norman H. Mellor ....(Mar) 264
Correction: Use of Steroids in Burn Care (Correspondence), David M. Heimbach .(May) 454

Correspondence:

Accidental Hypothermia: Hypoglycemia or Hyperglycemia, Philip Altus, Jack Hickman ....(May) 455
Reply, Faith Fitzgerald ....(May) 455
Alkalinization Therapy for Tricyclic Antidepressant Overdose:
Mary Linda Stotter ....(May) 450
Michael Callaham ....(May) 450
Reply, Jerome R. Hoffman, Charles R. McElroy ....(May) 451
Ascorbic Acid [Vitamin C Serum Levels] and Nutrition, Michael S. Margoles ....(May) 452
Appropriateness Review: An Overview, Howard L. Lang ....(Mar) 265
Correspondence, Roy R. Deffebach ....(May) 456
Ave Atque Vale, George X. Trimble ....(Jun) 548
Coronary Bypass Operations, Norman H. Mellor ....(Mar) 264
Correction: Use of Steroids in Burn Care, David M. Heimbach ....(May) 454
Diagnosis of Human Pulmonary Dirofilariasis, Flavio Ciferri ....(Jun) 547
Diet Not Shown Effective in Psoriasis, Marvin Rapaport ....(Apr) 364
Gastrointestinal Barotrauma, Kenneth W. Kizer ....(May) 449
HAFE in Nepal, E. Y. Davis ....(Apr) 366
Health Care Rules and Regulations:
James M. Moorefield ....(Mar) 264
John M. Kenney ....(Mar) 265
High Altitude Flatus Expulsion (HAFE), Paul Auerbach, York E. Miller ....(Feb) 173
Correspondence:
E. Y. Davis ....(Apr) 366
Edward Geehr ....(May) 449
Kenneth Kizer ....(May) 449
Charles R. McElroy, Jerome R. Hoffman .(Jun) 546
Hypokalemia in the Syndrome of Inappropriate Secretion of Antiduretic Hormone [SIADH], Amin A. Nanji ....(May) 452
Hypophosphatemia: Correct Quantity of 50 Percent Magnesium Sulfate, Willis C. Triplett ....(Apr) 366
Reply, James P. Knochel ....(Apr) 366
Importance of Making Precise Medical Records in the 1980's. Samuel E. Spital ....(Feb) 169
Correspondence, Gary S. Brody ....(May) 453
Infirmaries: A Way to Reduce Medical Costs?, Ed Sargent ....(Apr) 364
Laboratory Evaluation of Neurosyphilis, James B. Peter ....(Apr) 365
Magnesium—It's About Time, Bernard Horn .(Jan) 72
Malaria in California:
Eric L. Stirling, Thomas Rowsell ....(Jun) 545
Charles J. Berletti ....(Jun) 545
Medicaid and the Medical Profession, Edward Palmer ....(Feb) 174
Medical Records as Instruments of Patient Care, Garry S. Brody ....(May) 453
More HAFE, Edward Geehr ....(May) 449
Mrs. Laennec and the Stethoscope, E. R. W. Fox ....(Jan) 73
Pericardial Effusion in Association With Giant Cell Arteritis, Harinder S. Garewal, Richard F. Uhlmann, Robert M. Bennett ..(Jan) 71
Platelet Dysfunction and Migraines, Lee Kudrow ....(May) 454
Reply by Author, Laurence A. Harker ...(May) 455

Possible Hazards of Nylon Athletic Shorts, Ed Sargent ..... (Feb) 168
Prevention of Nuclear War as a Medical Priority, Howard Kornfeld ..... (Apr) 365
Private Enterprise Physicians, An Endangered Species?, John M. Douglass ..... (Feb) 172
Problems Associated With Megadose Vitamin C Therapy, Towie Fong ..... (Mar) 264
Protection Against Loss of Bone and Fracture in Postmenopausal Women, Robert P. Heaney ..... (Jan) 74
Reply, Elmer E. Specht ..... (Jan) 75
Radiation Therapy for Skin Cancer, Ernst Epstein ..... (Feb) 167
Relapsing Fever Revisited, Stephan D. Fihn, Eric B. Larson ..... (Mar) 263
Still More HAFE, Charles R. McElroy, Jerome R. Hoffman .. (Jun) 546
Subacute Laetrile Intoxication, Richard C. Barnett, James Pointer, John Nimtz, Richard Beers . (Feb) 170
TdT Negative T-ALL, Stephen Lee, David Rosenbaum ..... (Feb) 168
Teaching the Pelvic Examination in an Internal Medicine Residency Program, Stephen Hamburger, Deborah Guthrie, P. Gail Smith, Kitt Shaffer ..... (Jun) 547
Therapy for Ankylosing Spondylitis, Richard A. Maun ..... (Apr) 364
Tonsillectomy and Adenoidectomy, Gordon Breitman ..... (Feb) 167
Treatment for Heatstroke Victims, Peter G. Hanson ..... (Feb) 167
Correction ..... (Jun) 548

Costs, see *Infirmaries*
[Cranial Nerve Palsies], see *Immunoglobulin D Myeloma*
Croakers' Dilemma—Should Prison Physicians Serve Prisons or Prisoners (Methical Ethics), Kim Marie Thorburn ..... (May) 457
Customer Satisfaction [Health Care] (Editorial) ..... (Mar) 261
Cyanide Poisoning in Man, see *Amygdalin Toxicity Studies*

D

Day-care Centers, see *Care of Mildly Ill Children*
Deficiency, see *Iron*
Deregulation and Governance in Health Care (Editorial) ..... (Jan) 54
Dermatology, see *Epitomes*
Diabetes Mellitus and Orthostatic Hypotension Resulting From Ingestion of Vacor rat poison—Endocrine and Autonomic Function Studies, Kenneth S. Peters, Theodore G. Tong, Kathleen Kutz, Neal L. Benowitz ..... (Jan) 65
Diagnosis of Human Pulmonary Dirofilariasis, Flavio Ciferri (Correspondence) ..... (Jun) 547
Diaphragm, see *Treatment of Agenesis*
[Diet], see *Iron Deficiency*
Diet Not Shown Effective in Psoriasis (Correspondence), Marvin Rapaport ..... (Apr) 364
Dirofilariasis, see *Human Pulmonary*
Disorders of Platelet Function—Mechanisms, Diagnosis and Management (Medical Progress), Lothar A. Huebsch, Laurence A. Harker . (Feb) 109
Editorial, James G. White ..... (Feb) 148
Correspondence, Lee Kudrow ..... (May) 454
Reply, Laurence A. Harker ..... (May) 455
Diverticular Disease of the Colon (Medical Staff Conference) ..... (Jun) 515
Doctors, see *Patients as*
[Dog Heartworm], see *Human Pulmonary Dirofilariasis*
[Drug Abuse], see *Heroin Addiction and Pregnancy*
[Drug Abuse], see *Physician Attitudes*
Drugs, see *Psychotherapeutic*
Drugs That Modify Platelet Function, see *Thrombosis—Part II* under *Specialty Conferences*
Dysrhythmia, see *Bicarbonate Therapy*

E

Editorials: (General and Scientific)

General:

Ascites, Frank L. Iber ..... (May) 438
Changing Cigarette, The [Smoking], John H. Holbrook ..... (Apr) 353
Customer Satisfaction [Health Care] ..... (Mar) 261
Deregulation and Governance in Health Care . (Jan) 54
Has the Public's Interest in Health Care Peaked? ..... (Feb) 149
Hopes and No Hopes for the Next Quadrennium ..... (Feb) 147
Iron Nutrition, Clement A. Finch ..... (Jun) 532
Of Gerontology, Geriatrics and Gereology .. (Mar) 258
Patients and Others as Doctors ..... (Apr) 350
Physicians' Fees—Not Too Bad a Record ... (Jan) 59
Welcome NMMS ..... (Apr) 348

Scientific:

Financial Aid for Medical Students ..... (May) 439
From Clubbing to Collagen, David C. Siegel . (Apr) 352
Is There Miscommunication About Private Practice? ..... (Jun) 533
It's Not Just How Low You Make It, but How You Make it Low [Hypophosphatemia], R. Curtis Morris, Jr ..... (Jan) 56
Measuring Blood Pressure in Young Patients, Shiela C. Mitchell ..... (Apr) 348
Of Gluts and Prices ..... (Jun) 532
Platelet Connection in Arteriosclerotic Disease, Arthur J. Moss ..... (Mar) 261
Platelets in Perspective, James G. White .... (Feb) 148
Prognosis After Myocardial Infarction, Stephen C. Achuff ..... (Jan) 55
Psychotherapeutic Drugs in Medical Practice, Leo E. Hollister ..... (Mar) 259
Violence by Handguns ..... (May) 438
Why Thrombolytic Therapy, Sol Sherry ..... (Feb) 149

[Electrical Injuries], see *Lightning Burns*

Epitomes of Progress:

Dermatology ..... (Jan) 43
Psychiatry ..... (Feb) 141
Radiology ..... (Mar) 248
Urology ..... (Apr) 342
Nuclear Medicine ..... (May) 433
Obstetrics and Gynecology ..... (Jun) 524

Esophageal Crura, see *Treatment of Agenesis*
Extrahepatic Biliary Duct Trauma—A Spectrum of Injuries, Todd B. Burt, James A. Nelson ..(Apr) 283

F

Fat, see *Role of Dietary*
Fees, see *Physicians'*
Fever, see *Relapsing*
Fever of Undetermined Origin, see *Retroperitoneal Fibrosis*
Fibrinolytic Agents, see *Use of*
Fibrosis, see *Retroperitoneal*
Fibrositis—Misnomer for a Common Rheumatic Disorder (Medical Progress), Robert M. Bennett .....(May) 405
Financial Aid for Medical Students (Editorial) .....(May) 439
Fine-Needle Aspiration Biopsy in the Management of Thyroid Nodules, Theodore R. Miller, John S. Abele, Francis S. Greenspan .....(Mar) 198
Follow-Up of Patients. see *Myocardial Infarction*
Fourteen Fallacies About Patient Package Inserts (Informed Opinion), Jere Goyan .....(May) 463

From a Medical Student:

Preventive Medicine in Practice: The State of the Art, David J. Maron .....(Apr) 367

From Clubbing to Collagen (Editorial), Robert C. Siegel .....(Apr) 352

G

Gastrointestinal Barotrauma (Correspondence), Kenneth W. Kizer .....(May) 449
[Gastrointestinal Bleeding], see *Aortoenteric Fistula*
Gluts and Prices, see *Of*
Governance, see *Deregulation*
Great Imitator, Syphilis, The (Medical Staff Conference) .....(May) 424
Gynecology, see *Obstetrics and*
Guns, see *Violence by Hand-*
Gunshot Penetrating Injuries of the Descending Thoracic Aorta, Charles H. Dart, Jr, Howard E. Braitman, Somboon Larlarb .(May) 442
Gynecology, Obstetrics and, see *Epitomes*

H

HAFE, see *High Altitude Flatus*
HAFE, see *Still More*
HAFE in Nepal (Correspondence), E. Y. Davis .....(Apr) 366
Halsted Mastectomy: Present Illness and Past History (Special Article), Cordelia Shaw Bland ...(Jun) 549
Has the Public's Interest in Health Care Peaked? (Editorial) .....(Feb) 149
[Health Care], see *Customer Satisfaction*
Health Care, see *Deregulation*
Health Issues for Women, see *Notes on*

Health Care Delivery:

Medical and Health Care in State Residential Institutions for Children and Youths: Report of Survey Findings in Five Hospitals, Committee on Children With Handicaps, Northern California Chapter, American Academy of Pediatrics—Albert C. Fremont, Helen M. Wallace, Lucy Crain, Krist A. Biakanja, Nancy Roizen .....(Jan) 80
Care of Mildly Ill Children Enrolled in Day-care Centers—Management by Parents and by Trained Home Workers, Albert Chang, George Kelso, Marcia Harris, Alice Jordan .....(Feb) 181

Health Care Peaked?, see *Has the Public's Interest*
Health Care Rules and Regulations (Correspondence):
James M. Moorefield .....(Mar) 264
John M. Kenney .....(Mar) 265
Heart, see *Aging*
Heatstroke, see *Treatment for*
Hemolytic-Uremic Syndrome, Craig Brasher, Richard L. Siegler .....(Mar) 193
Hepatitis, see *Abornmal Aminopyrine Metabolism*
Hepatosplenomegaly in a Woman, see *Jaundice*
Heroin Addiction and Pregnancy, see *Specialty Conferences*
High Altitude Flatus Explosion (HAFE) (Correspondence), Paul Auerbach, York E. Miller .....(Feb) 173
Correspondence:
E. Y. Davis .....(Apr) 366
Edward Geehr .....(May) 449
Kenneth Kizer .....(May) 449
Charles R. McElroy, Jerome R. Hoffman .(Jun) 546
History, see *Halsted Mastectomy and Past*
Hopes and No Hopes for the Next Quadrennium (Editorial) .....(Feb) 147
Hormone, Antidiuretic, see *Hypokalemia*
Human Pulmonary Dirofilariasis in the West, Flavio Ciferri .....(Feb) 158
Addendum: Dx of HPD, Flavio Ciferri ...(Jun) 547
Hydrothorax, see *Unilateral*
Hyperglycemia, see *Accidental Hypothermia*
[Hypertension] in Infants, Children and Adolescents, see *Blood Pressure*
Hypoglycemia, see *Accidental Hypothermia*
Hypokalemia in the Syndrome of Inappropriate Secretion of Antidiuretic Hormone [SIADH], (Correspondence), Amin A. Nanji .....(May) 452
Hypophosphatemia (Nutrition in Medicine), James P. Knochel .....(Jan) 15
Editorial, R. Curtis Morris, Jr .....(Jan) 56
Correspondence, Willis C. Triplett .....(Apr) 366
Reply, James P. Knochel .....(Apr) 366
Hypophosphatemia: Correct Quantity of 50 Percent Magnesium (Correspondence), Willis C. Triplett .....(Apr) 366
Reply, James P. Knochel .....(Apr) 366
Hypotension, see *Bicarbonate Therapy*
Hypothermia, see *Accidental* and *Severe Lactic Acidosis*
Hypothermia, see *Accidental*

I

Idiopathic Hypertrophic Osteoarthropathy (Pachydermoperiostosis), David A. Herbert, W. Jeffrey Fessel .....(Apr) 354
Editorial, Robert C. Siegel .....(Apr) 352
Ill Children Enrolled in Day-care Centers, see *Care of*
[Immunodeficiency], see *Lung Involvement*

Immunoglobulin D Myeloma: Report of a Case With Unusual Neurological Complications, Vincent Caggiano, Surl L. Nielsen, Frank J. Glassy, David F. Dozier, Jr .....(Feb) 153
Importance of Making Precise Medical Records in the 1980's (Correspondence), Samuel E. Spital .....(Feb) 169
Correspondence, Garry S. Brody .....(May) 453
Impotence, see *Penile Revascularization*
[Incest], see *Notes on Health Issues*
Infections, see *Obstetric*

Information:

Neurosyphilis: An Update, Roger P. Simon .(Jan) 87
Correspondence, James B. Peter .....(Apr) 365
Aging Heart, The—Observations in Patients 40 Years Old and Older, Richard S. Cosby, Mary May, Adrian Mirea, James A. Peterson .....(Feb) 186
Xeromammography Versus Screen-Film Mammography—Pros and Cons of the Two Techniques, Edward A. Sickles .....(Mar) 273
Advances in Burn Care, David H. Heimbach, Loren H. Engrav, Janet A. Marvin .....(Mar) 274
Correction: Use of Steroids in Burn Care (Correspondence), David M. Heimbach .(May) 454
Notes on Health Issues for Women:
Understanding the Medical and Psychological Aspects of Rape, Fran Pepitone-Rockwell .....(Jun) 556
Battered Wives, Donna M. Moore .....(Jun) 557
Women in Medicine—Myths and Realities, Fran Pepitone-Rockwell, Don A. Rockwell .....(Jun) 559
Incest, Sandra Baker .....(Jun) 560

Informed Opinion:

Fourteen Fallacies About Patient Package Inserts, Jere Goyan .....(May) 463

Infirmaries: A Way to Reduce Medical Costs? (Correspondence), Ed Sargent .....(Apr) 364
Institutions for Children and Youths, see *Medical and Health Care*
Intrapleural Rupture, see *Bronchogenic Cyst*
Internal Medicine Residency, see *Teaching Pelvic Examination*
Iron Deficiency: Diagnosis and Treatment (Nutrition in Medicine), Peter R. Dallman .....(Jun) 496
Editorial, Clement A. Finch .....(Jun) 532
Iron Nutrition (Editorial), Clement A. Finch .....(Jun) 532
Is There Miscommunication About Private Practice? (Editorial) .....(Jun) 533
It's Not Just How Low You Make It, But How You Make It Low [Hypophosphatemia] (Editorial), R. Curtis Morris, Jr. .....(Jan) 56

J

Jaundice, Hepatosplenomegaly and Liver Failure in a 60-Year-Old Woman (UCLA), see *Specialty Conferences*
[Joint] Disorder, see *Fibrositis*
[Joggers], see *Possible Hazards of Nylon Athletic Shorts*

K

[Kawasaki Disease], see *Toxic Shock Syndrome*

L

Laboratory Evaluation of Neurosyphilis (Correspondence), James B. Peter .....(Apr) 365
Lactic Acidosis and Hypothermia, see *Severe*
Laennec, Mrs., and the Stethoscope (Correspondence), E. R. W. Fox .....(Jan) 73
[Laetrile], see *Amygdalin Toxicity Studies*
Laetrile Intoxication, see *Subacute*
Lens Implantation, Intraocular, see *Recent Advances*
Leukemia, Acute Lymphocytic, see *TdT Negative T-ALL*
Lightning Burns, Virginia L. McCrady-Kahn, Arthur M. Kahn .....(Mar) 215
Lipoprotein Metabolism, see *Role of Dietary Fat*
Liver Biopsy, see *Bleeding After*
Liver Failure, see *Jaundice*
Lung Cancer, see *Radiologic Error*
Lung Involvement in Progressive Vaccinia, David S. Chudwin, Morton J. Cowan, Diane W. Wara, Alan C. Johnson .....(May) 446

M

Magnesium—It's About Time (Correspondence), Bernard Horn .....(Jan) 72
Malaria in California (Correspondence): Eric L. Stirling, Thomas Rowsell .....(Jun) 545
Charles J. Berletti .....(Jun) 545
Malignant Disease, see *Breast Reconstruction*
Mammography, see *Xeromammography Versus Screen-Film*
Mastectomy, see *Halsted*
Measuring Blood Pressure in Young Patients (Editorial), Shiela C. Mitchell .....(Apr) 348
Medicaid and the Medical Profession (Correspondence), Edward Palmer .....(Feb) 174
Medical and Health Care in State Residential Institutions for Children and Youths—Report of Survey Findings in Five Hospitals (Health Care Delivery), Committee on Children With Handicaps, Northern California Chapter, American Academy of Pediatrics—Albert C. Fremont, Helen M. Wallace, Lucy Crain, Krist A. Biakanja, Nancy Roizen .....(Jan) 80

Medical Ethics:

Croakers' Dilemma—Should Prison Physicians Serve Prisons or Prisoners?, Kim Marie Thorburn .....(May) 457

Medical Practice, see *Psychopharmacology in*
Medical Profession, see *Medicaid*

Medical Progress:

Disorders of Platelet Function—Mechanisms, Diagnosis and Management, Lothar B. Huebsch, Laurence A. Harker .....(Feb) 109
Editorial, James G. White .....(Feb) 148
Correspondence, Lee Kudrow .....(May) 454
Reply, Laurence A. Harker .....(May) 455

Psychopharmacology in Medical Practice—The Benefits and the Risks, Robert L. Sack, James H. Shore ..... (Mar) 223
Editorial, Leo E. Hollister ..... (Mar) 259
Blood Pressure in Infants, Children and Adolescents, Arthur J. Moss ..... (Apr) 296
Editorial, Shiela C. Mitchell ..... (Apr) 348
Fibrositis—Misnomer for a Common Rheumatic Disorder, Robert M. Bennett ..... (May) 405

Medical Records, Precise, see *Importance*
Medical Records as Instruments of Patient Care (Correspondence), Garry S. Brody ..... (May) 453

Medical Staff Conferences:

Role of Dietary Fat and Cholesterol in Atherosclerosis and Lipoprotein Metabolism, Chief Discussant: Robert W. Mahley ..... (Jan) 34
Seronegative Spondylarthritis, Chief Discussant: David Wofsy ..... (Feb) 128
Correspondence, Richard A. Maun ..... (Apr) 364
Aortoenteric Fistula Gastrointestinal Bleeding, Chief Discussant: Lawrence M. Tierney, Jr. .... (May) 242
Newer Antiarrhythmic Drugs, Chief Discussant: David S. Hess ..... (Apr) 333
Great Imitator, Syphilis, Chief Discussant: Faith Fitzgerald ..... (May) 424
Diverticular Disease of the Colon, Chief Discussant: John P. Cello ..... (Jun) 515

Medicine, see *Preventive*

Medicine in Perspective:

American Physician in Rural West Africa, William L. Minkowski ..... (Mar) 267

Megadose Vitamin C, see *Problems Associated With*
[Mental Illness], see *Physician Attitudes*
Mesothelioma: Current Perspectives, Roy A. Taylor, Lloyd P. Johnson ..... (May) 379
Metabolism in . . . Hepatitis, see *Abnormal Aminopyrine*
Methemoglobinemia, see *Acquired*
Migraines, see *Platelet Dysfunction*
More HAFE (Correspondence), Edward Geehr ..... (May) 449
Mrs. Laennec and the Stethoscope (Correspondence), E. R. W. Fox ..... (Jan) 73
Myeloma, see *Immunoglobulin D*
Myocardial Infarction—A Five-Year Follow-Up of Patients, Karla K. Kishpaugh, Marilyn H. Ford, C. Hilmon Castle, James C. Reading ..... (Jan) 1
Editorial, Stephen C. Achuff ..... (Jan) 55
Myocardial Infarction, see *Prognosis After*

N

Nasopharyngeal Carcinoma, see *Obstructive Sleep Apnea Syndrome*
Nepal, see *HAFE*
Neurological Complications, see *Immunoglobulin D Myeloma*
Neurosyphilis, see *Laboratory Evaluation*
Neurosyphilis: An Update (Information), Roger P. Simon ..... (Jan) 87
Correspondence, James B. Peter ..... (Apr) 365
[New Mexico Medical Society], see *Welcome NMMS*
Newer Antiarrhythmic Drugs (Medical Staff Conference) ..... (Apr) 333
[Nitrate, Dietary], see *Acquired Methemoglobinemia*

Notes on Health Issues for Women (Information):

Understanding the Medical and Psychological Aspects of Rape, Fran Pepitone-Rockwell .(Jun) 556
Battered Wives, Donna M. Moore ..... (Jun) 557
Women in Medicine—Myths and Realities, Fran Pepitone-Rockwell, Don A. Rockwell .(Jun) 559
Incest, Sandra Baker ..... (Jun) 560

Nuclear Medicine, see *Epitomes*
Nuclear War, see *Prevention of*
Nutrition, see *Ascorbic Acid*
[Nutrition], see *Magnesium*

Nutrition in Medicine:

Hypophosphatemia, James P. Knochel ..... (Jan) 15
Editorial, R. Curtis Morris, Jr. ..... (Jan) 56
Correspondence, Willis C. Triplett ..... (Apr) 366
Reply, James P. Knochel ..... (Apr) 366
Iron Deficiency: Diagnosis and Treatment, Peter R. Dallman ..... (Jun) 496
Editorial, Clement A. Finch ..... (Jun) 532

O

Obstetric Infections, Henry A. Oster ..... (May) 394
Obstetrics and Gynecology, see *Epitomes*
Obstetrics and Gynecology: Considerations in Career Selection, Edmund S. Petrilli ..... (Jan) 77
Obstructive Sleep Apnea Syndrome Associated With Nasopharyngeal Carcinoma, Frank M. Moses, Jon H. Buscemi ..... (Jan) 69
Of Gerontology, Geriatrics and Gereology (Editorial) ..... (Mar) 258
Of Gluts and Prices (Editorial) ..... (Jun) 532
Orthostatic Hypotension From Rat Poison, see *Diabetes Mellitus*
Osteoarthropathy, see *Idiopathic Hypertrophic*
Overdose, see *Alkalinization Therapy*
Overdose, see *Bicarbonate Therapy*

P

Pachydermoperiostosis, see *Idiopathic Hypertrophic*
Pacing, Ventricular, see *Control of*
Package Inserts, Patient, see *Fourteen Fallacies*
Patients as Doctors (Editorial) ..... (Apr) 350
Patient Care, see *Medical Records*
Patient Package Inserts, see *Fourteen Fallacies*
Pelvic Examination in Internal Medicine Residency Program, see *Teaching*
Penile Revascularization in the Treatment of Impotence, Ira D. Sharlip ..... (Mar) 206
Pericardial Effusion in Association With Giant Cell Arteritis (Correspondence), Harinder S. Garewal, Richard F. Uhlmann, Robert M. Bennett ..(Jan) 71
Phacoemulsification, see *Recent Advances in Cataract*
[Phosphate Deficiency], see *Hypophosphatemia*
Physician Attitudes Toward Distressed Colleagues, John N. Chappel ..... (Feb) 175

Physicians, see *Private Enterprise*
Physicians' Fees—Not Too Bad a Record (Editorial) ..... (Jan) 59
Pittsburgh Pneumonia Agent, see *Primary Isolation*
Platelet Connection in Arteriosclerotic Disease (Editorial), Arthur J. Moss ..... (Mar) 261
Platelet Dysfunction and Migraines (Correspondence), Lee Kudrow ..... (May) 454
Reply by Author, Laurence A. Harker ... (May) 455
Platelet Function, see *Disorders of*
Platelet Function, see *Thrombosis—Part II* under *Specialty Conferences*
Platelets in Perspective (Editorial), James G. White ..... (Feb) 148
Pneumonia Agent, see *Primary Isolation*
Poison, Rat, see *Diabetes Mellitus . . . Resulting From Ingestion*
Poisoning, see *Amygdalin Toxicity Studies*
Possible Hazards of Nylon Athletic Shorts (Correspondence), Ed Sargent ..... (Feb) 168
Postmenopause, see *Protection . . . Loss of Bone*
Practice, see *Preventive Medicine in*
Pregnancy, see *Heroin Addiction and*
[Pregnancy], see *Obstetric Infections*
Preoperative Management of Proximal Lesions of the Left Coronary Artery System: Surgical Implications, Hans J. Krebber, Robert J. Szarnicki, J. Donald Hill ..... (Jun) 491
Prevention of Nuclear War as a Medical Priority (Correspondence), Howard Kornfeld .... (Apr) 365
Preventive Medicine in Practice: The State of the Art (From a Medical Student), David J. Maron ..... (Apr) 367
Prices, see *Of Gluts*
Primary Isolation of a New Strain of the TATLOCK/Pittsburgh Pneumonia Agent, Elizabeth A. Donegan, Marlene M. Deal, M. Claire Melanephy, Lester G. Cordes III, C. Wayne Moss, Vincent G. Pons, George F. Brooks ..... (May) 384
Prison Physicians, see *Croakers' Dilemma*
Private Enterprise Physicians, An Endangered Species? (Correspondence), John M. Douglass ..... (Feb) 172
Private Practice, see *Is There Miscommunication*
Problems Associated With Megadose Vitamin C Therapy (Correspondence) ..... (Mar) 264
Prognosis After Myocardial Infarction (Editorial), Stephen C. Achuff ..... (Jan) 55
[Propranolol], see *Preoperative Management . . . Coronary Artery*
Pros and Cons, see *Xeromammography*
Protection Against Loss of Bone and Fracture in Postmenopausal Women (Correspondence), Robert P. Heaney ..... (Jan) 74
Reply, Elmer E. Specht ..... (Jan) 75
[Protein Levels], see *Ascites*
Psoriasis, see *Diet Not Shown Effective in*
[Psoriatic Arthritis], see *Seronegative Spondylarthritis*
Psychiatry, see *Epitomes*
Psychopharmacology in Medical Practice—The Benefits and the Risks (Medical Progress), Robert L. Sack, James H. Shore ..... (Mar) 223
Editorial, Leo E. Hollister ..... (Mar) 259
Psychotherapeutic Drugs in Medical Practice (Editorial), Leo E. Hollister ..... (Mar) 259
Pulmonary Dirofilariasis, see *Human*

R

Radiation Therapy for Skin Cancer (Correspondence), Ernst Epstein ..... (Feb) 167
Radiologic Error in Patients With Lung Cancer, John V. Forrest, Paul J. Friedman ..... (Jun) 485
Radiology, see *Epitomes*
Radionuclide Imaging Techniques, see *Unilateral Hydrothorax*
[Rape], see *Notes on Health Issues for Women*
Rat Poison, see *Diabetes Mellitus and Hypotension*
Recent Advances in Cataract Operations—Phacoemulsification, Intraocular Lens Implantation and Prolonged Wear Soft Contact Lenses, James J. Salz ..... (Apr) 290
Reconstruction, see *Breast*
Regulations, see *Health Care Rules and*
[Reiter Disease], see *Seronegative Spondylarthritis*
Relapsing Fever Revisited (Correspondence), Stephan D. Fihn, Eric B. Larson ..... (Mar) 263
[Renal Failure], see *Hemolytic-Uremic Syndrome*
Retroperitoneal Fibrosis as a Cause of Fever of Undetermined Origin, William E. Byrd, Robert E. Hunt, Richard Burgess ..... (Apr) 357
Editorial, Robert C. Siegel ..... (Apr) 352
Revascularization, see *Penile*
Rheumatic Disorder, see *Fibrositis*
Risks, see *Psychopharmacology in Medical Practice*
Role of Dietary Fat and Cholesterol in Atherosclerosis and Lipoprotein Metabolism (Medical Staff Conference) ..... (Jan) 34
[Runners], see *Possible Hazards of Nylon Athletic Shorts*
Rupture, Intrapleural, see *Bronchogenic Cyst*
Rural West Africa, see *American Physician in*

S

Sensitization, see *Autoerythrocyte*
Seronegative Spondylarthritis (Medical Staff Conference) ..... (Feb) 134
Correspondence, Richard A. Maun ..... (Apr) 364
Severe Lactic Acidosis and Hypothermia, Brian J. Murray ..... (Feb) 162
[Sexual Dysfunction], see *Penile Revascularization*
SIADH, see *Hypokalemia*
[Silver Nitrate for Burn Wounds], see *Acquired Methemoglobinemia*
Skin Cancer, see *Radiation Therapy*
Sleep Apnea Syndrome, see *Obstructive*
[Smallpox] Vaccinia, see *Lung Involvement*
[Smoking], see *Changing Cigarette*

Special Articles:

Obstetrics and Gynecology: Considerations in Career Selection, Edmund S. Petrilli ..... (Jan) 77
Physician Attitudes Toward Distressed Colleagues, John N. Chappel ..... (Feb) 175
Halsted Mastectomy: Present Illness and Past History, Cordelia Shaw Bland ..... (Jun) 549

Specialty Conferences:

Jaundice, Hepatosplenomegaly and Liver Failure in a 60-Year-Old Woman (Clinicopathologic Conference from UCLA), Discussants: David J. Campisi, Charles R. McElroy, J. Michael Criley, Frederick Gilkey ..... (Jan) 27

Use of Fibrinolytic Agents (Stanford University), Moderator: Stanley L. Schrier; Participants: Arthur A. Sasahara, Robert T. Wall, Christina B. Harbury .....(Feb) 128
Editorial, Sol Sherry .....(Feb) 149
Thrombosis: Its Role and Prevention in Cardiovascular Events (Hematology-Oncology Conference, University of Washington, Seattle):
Part I: Concepts of Thrombogenesis and Its Prevention, Laurence A. Harker .....(Mar) 234
Part II:
Anticoagulants and Thrombolytic Agents in Cardiovascular Disease, Arthur R. Thompson .....(Apr) 315
Drugs That Modify Platelet Function, John M. Harlan .....(Apr) 325
Editorial, Arthur J. Moss .....(Mar) 261
Ascites (USC School of Medicine and Rancho Los Amigos Hospital, Downey), Participants: Karen L. Lindsay, Telfer B. Reynolds, John C. Hoefs, Miguel E. Sanmarco .....(May) 414
Editorial, Frank L. Iber .....(May) 438
Heroin Addiction and Pregnancy (UC, Los Angeles, Department of Medicine, Interdepartmental Conference), Moderator: Richard A. Bashore; Discussants: James S. Ketchum, Klaus J. Staisch, Cynthia T. Barrett, Emery G. Zimmerman .(Jun) 506

Steroids, see *Correction: Use of*
Stethoscope, see *Mrs. Laennec and*
Still More HAFE (Correspondence), Charles R. McElroy, Jerome R. Hoffman ..(Jun) 546
[Streptokinase], see *Use of Fibrinolytic Agents*
Students, see *Financial Aid for Medical*
Subacute Laetrile Intoxication (Correspondence), Richard C. Barnett, James Pointer, John Nimtz, Richard Beers .....(Feb) 170
Syndrome, see *Hemolytic-Uremic*
Syndrome [SIADH], see *Hypokalemia*
Syphilis, see *Great Imitator* and *Neurosyphilis*

T

[Tampon Users], see *Toxic Shock Syndrome*
TATLOCK/Pittsburgh Pneumonia Agent, see *Primary Isolation*
TdT Negative T-ALL [Acute Lymphocytic Leukemia] (Correspondence), Stephen Lee, David Rosenbaum .....(Feb) 168
Teaching the Pelvic Examination in an Internal Medicine Residency Program (Correspondence), Stephen Hamburger, Deborah Guthrie, P. Gail Smith, Kitt Shaffer .....(Jun) 547
Thoracic Aorta, see *Gunshot Penetrating Injuries*
Thrombogenesis and Its Prevention, see *Thrombosis—Part I* under *Specialty Conferences*
Thrombolytic Agents, see *Thrombosis—Part II* under *Specialty Conferences*
Thrombolytic Therapy, see *Why*
Thrombosis: Role and Prevention in Cardiovascular Events, (University of Washington), see *Specialty Conferences*
Thyroid Nodule, see *Fine-Needle . . . Biopsy*
Tonsillectomy and Adenoidectomy (Correspondence), Gordon Breitman .....(Feb) 167
Toxic Shock Syndrome, Martha H. Tanner, Barbara J. Pierce, DeVon C Hale .....(Jun) 477
Toxic Shock Syndrome in a 19-Year-Old Woman, Mary Rachel Faris, William F. Skeen, Lisa A. Abrahams .....(Jun) 535
Trauma, see *Extrahepatic Biliary Duct*
Treatment for Heatstroke Victims (Correspondence), Peter G. Hanson .....(Feb) 167
Correction .....(Jun) 548
Treatment of Agenesis of the Diaphragm and Esophageal Crura—An 18-Year Follow-up, J. Ordie Shaffer .....(Apr) 361
Tricyclic Antidepressant Overdose, see *Alkalinization Therapy*
Tricyclic Antidepressant Overdose, see *Bicarbonate Therapy*
[Tropical Diseases], see *Malaria in California*

U

Understanding the Medical and Psychological Aspects of Rape, see *Notes on Health Issues*
Unilateral Hydrothorax Secondary to Ascites—Demonstration by a Noninvasive Radionuclide Imaging Technique, Kokila Vyas, Gerbail T. Krishnamurthy .(Mar) 220
[Urinary Tract] Infections, see *Obstetric*
[Urokinase], see *Use of Fibrinolytic Agents*
Urology, see *Epitomes*
Use of Fibrinolytic Agents (Stanford University), see *Specialty Conferences*

V

Vaccinia, see *Lung Involvement*
[Venereal Disease], see *Great Imitator, Syphilis*
[Venereal Disease], see *Neurosyphilis*
Ventricular Ectopy, see *Control of Refractory*
Violence by Handguns (Editorial) .....(May) 438
[Viral] Infections, see *Obstetric*
[Vitamin C Serum Levels], see *Ascorbic Acid*
Vitamin C Therapy, Megadose, see *Problems Associated*

W

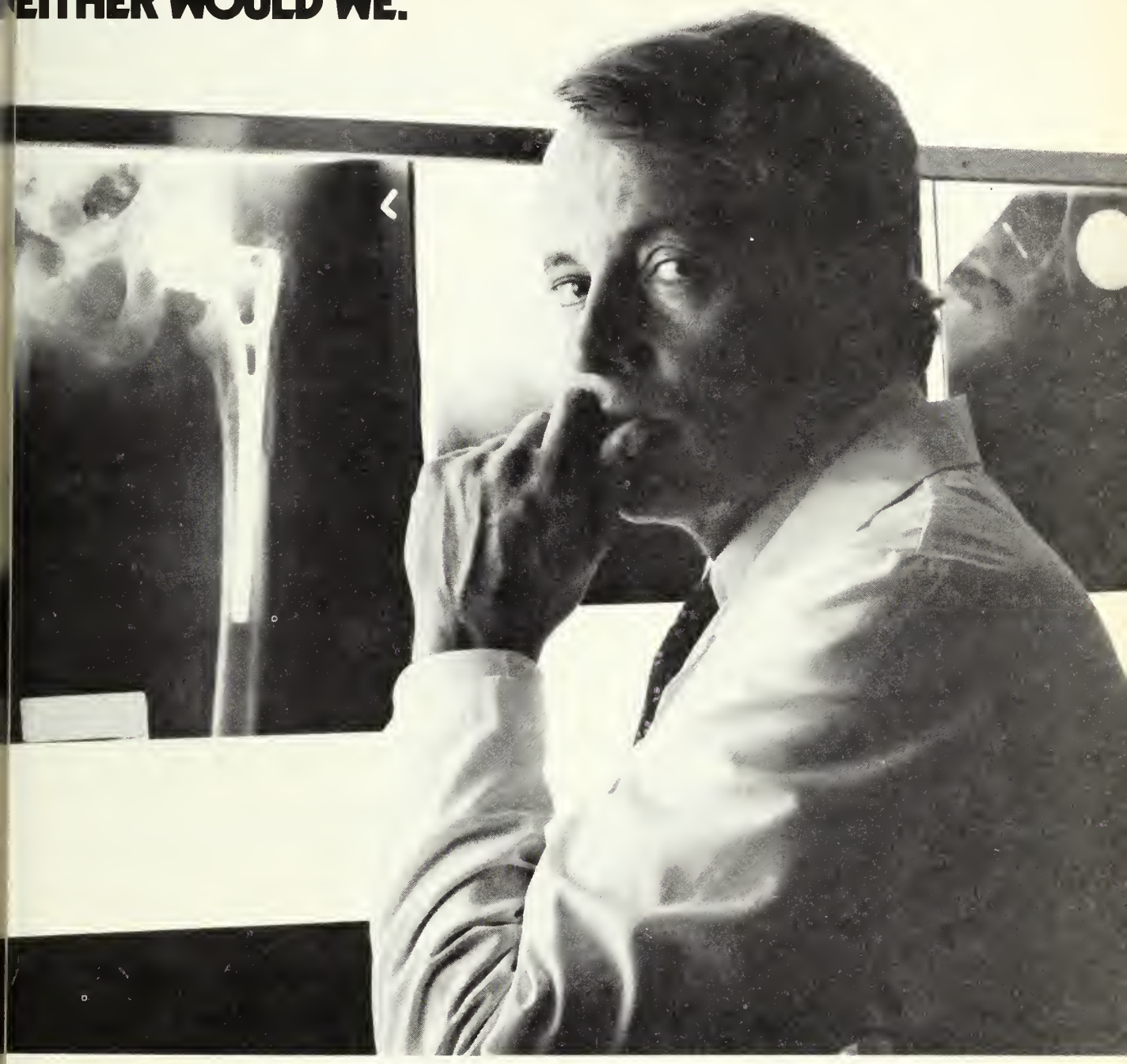
Welcome NMMS [New Mexico Medical Society] (Editorial) .....(Apr) 348
Why Thrombolytic Therapy (Editorial), Sol Sherry .....(Feb) 149
Woman, see *Jaundice*
Women, see *Notes on Health Issues*
Women, Postmenopausal, see *Protection Against Loss of Bone*
Women in Medicine, see *Notes on Health Issues*

X,Y,Z

Xeromammography Versus Screen-Film Mammography—Pros and Cons of the Two Techniques (Information), Edward A. Sickles .....(Mar) 273
Youths, see *Medical and Health Care in Institutions*

OULD YOU GUARANTEE THERE WON'T BE PROBLEMS VER THE NEXT 5 YEARS?

EITHER WOULD WE.



Responsible physicians know that despite sound medical judgment and specialized skills, their prognoses are often subject to uncertainty.

You must make allowances for potential adversity and you should expect your professional liability insurance company to do the same.

Responsible medical malpractice insurers, like The Doctors' Company, know that their policyholders' long-range interests are best protected by financial strength and solvency. That's why we maintain the largest surplus of all the doctor-owned malpractice insurers in the western United States. That's why our earned premium to surplus ratio is the most favorable of all these companies. And that's why we continue to collect surplus contributions from new members.

Future results can't be guaranteed, in the fragile art of medicine or in the volatile business of malpractice insurance. Our allowance for adversity is surplus.

For details about our program, call or write: The Doctors' Company, 233 Wilshire Blvd., Santa Monica, CA 90401. (213) 451-9936. Toll free, (800) 352-7271. Outside California, (800) 421-2368.

THE DOCTORS' COMPANY

AN INTERINSURANCE EXCHANGE
OFFERING MEDICAL MALPRACTICE INSURANCE
TO DOCTORS IN
CALIFORNIA, NEVADA, WYOMING AND MONTANA

Classified Advertisements

The rate for each insertion is **4.00 per line** (average six words per line) **with five line minimum.**

Box number charge: $2.00 each month.

Classified display rates $40.00 per inch.

Copy for classified advertisements should be received not later than **the fifth of the month preceding issue. All copy must be typed or printed.** • Classified advertisers using Box Numbers forbid the disclosure of their identity. Your inquiries in writing will be forwarded to Box Number advertisers. The right is reserved to reject or modify all classified advertising copy in conformity with the rules of the Advertising Committee.

Please Type or Print Advertising Copy

CLASSIFIED ADVERTISEMENTS ARE PAYABLE IN ADVANCE

PHYSICIANS WANTED

ORTHOPEDIC SURGEON to join multispecialty group in Mt. Vernon, Washington. The Medical Center has outstanding x-ray facilities and is located across the street from a 126-bed hospital. Stockholder status available after one year. Guaranteed first year salary and liberal fringe benefits. On call coverage available. Position currently availabe. Contact Shane Spray, Administrator, Skagit Valley Medical Center, 1400 E. Kincaid, Mt. Vernon, WA 98273. Telephone (206) 428-2524.

Southern California Practice Opportunities

Humana, the world's largest hospital company, owns and operates 11 hospitals in both Los Angeles and Orange Counties. While these areas are, for the most part, heavily doctored, we can pinpoint needs for your specialty in our hospitals and communities.

We are seeking individuals in:

FAMILY PRACTICE
ORTHOPEDIC SURGERY
PEDIATRICS
ENT
INTERNAL MEDICINE
OB/GYN
INFECTIOUS DISEASES

For further information about these excellent practice opportunities call or write:

Gordon Crawford
Manager, Physician Recruitment

Toll-Free: 800-626-1590
Collect: 502-561-2300

Humana
The Hospital Company
1 Riverfront Plaza
Dept. N-6
Louisville, Kentucky 40201

PHYSICIANS WANTED

CALIFORNIA—FAMILY PRACTITIONERS/INTERNISTS needed for primary care group practices in fast-growing areas. Excellent professional support staff, modern facilities, percentage of gross income with guaranteed minimum income. Benefits include: Paid malpractice, health and life insurance, CME leave, etc. Send CV to S. Lee, Medicenters, P.O. Box 8013, Fresno, CA 93747. (209) 252-1618.

INTERNIST: Board Certied or eligible internist, to join well-established 3-man group of internists in San Jose, California. Office near excellent general hospital. Guaranteed salary first year. Incremental partnership thereafter. Send CV to Box 6196, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

ORTHOPEDIC SURGEON—to join 45 person multi-specialty group with four locations in San Diego. Board certified or eligible. Full clinical services available. CME approved group. Partnership possible in (2) years. Guaranteed salary first (2) years with excellent future opportunity. Start immediately. Rees-Stealy Medical Group, 2001 4th Ave., San Diego, CA 92101. (714) 234-6261, H. D. Peabody, MD.

CHEST PHYSICIAN—Position available for full-time chest physician in Pulmonary Disease Service. Requiring qualifications in clinical management, laboratory supervision, consultation, fiberoptic bronchoscopy, and teaching involvement with medical students, interns, and residents. American Board of Internal Medicine certification or eligibility, and California State license necessary. Completion of pulmonary Fellowship desirable. Salary and university faculty appointment negotiable according to credentials. Equal opportunity employer—Women and minority groups invited to apply. If interested, please submit curriculum vitae to: D. Armin Fischer, MD, Rancho Los Amigos Hospital, 7601 E. Imperial Hwy., Room 16, Bldg. 500, Downey, CA 90242.

SAN FRANCISCO BAY AREA: Three-man Family Practice group seek recent board-certified Family Practitioner for busy office. Attractive salary plus incentive, full fringes, 6 weeks vacation, and C.M.E. Send résumé to Philip R. Hines, MD, Inc., 220 Hospital Dr., Vallejo, CA 94590.

(Continued on Page 36)

MEDICAL DIRECTOR

Opportunity in Japan

If you have been seeking an opportunity to return to Japan, this is the time to join Pfizer Taito. This Tokyo-based division of Pfizer International has an opening for a physician with clinical experience and a background in internal medicine. The Medical Director's responsibilities include the development, assessment, and evaluation of new products for the Japanese market. Japanese citizenship is required.

We offer an excellent salary and benefits program, plus paid relocation expenses. If interested, please send résumé in confidence to: **Mr. J. M. Rocco, Manager, Employment, Pfizer Inc., 235 East 42nd Street, New York, N.Y. 10017.**

Pfizer

An equal opportunity employer

MEDICAL ADVISOR

Blue Cross of Southern California is seeking an energetic Physician interested in a stimulating and demanding career in the administrative aspects of medicine. Successful candidate will provide medical guidance to subordinate consultants, plan and coordinate review activities, review claims and their documentation & advise & assist the Vice President & Medical Director in medical policy matters.

The position requires a state license. Ideally the candidate will be specialty trained, with both an interest and background in utilization review and review of professional claims for medical necessity, however we are prepared for comprehensive on the job training.

We offer a congenial professional environment, good salary and a complete benefit package.

Please send resume to:

Jacque Boutin

Blue Cross
of Southern California
Employment Department
21555 Oxnard Street
Woodland Hills, CA
91367
(213) 703-2220

Affirmative Action Employer
Equal Opportunity
Employer M/F/H

Leadership

It took time to achieve it
It takes dedication to keep it

Purepac became the largest generic drug manufacturing facility in the United States by providing high quality generic pharmaceuticals at the lowest possible cost. We know that to be on top tomorrow, we've got to stay a few steps ahead today. Here are some of the steps we've already taken:

- **Full-time Medical Vice President with Supporting PhD Staff**
- **ANDA/Patent Review Departments**
- **State Formulary Manager**
- **Regulatory Affairs Department**
- **Comprehensive Advertising and Marketing Support Programs**

It took Purepac 50 years to achieve this leadership position. And we're determined to provide you with even more quality products and dedicated services in the next 50 years.

PUREPAC PHARMACEUTICAL CO.
Division of Kalipharma, Inc., Elizabeth, N.J. 07207

1930-1981
Celebrating over 50 years of industry leadership.

GN-1080

(Continued from Page 34)

PHYSICIANS WANTED

NEBRASKA EMERGENCY MEDICINE: Directorships and clinical positions available in several moderate volume emergency departments located in the western and central portions of the state. Excellent guaranteed income, plus additional stipend for directors' duties. Professional liability insurance provided; flexible scheduling without on-call involvement. For details, for ward credentials in confidence to William Salmo, Chase Stone Center, Holly Sugar Building, Suite 1070, Colorado Springs, CO 80903; or call tolifree 1 (800) 525-3681 (within Colorado call collect (303) 471-4981).

DIRECTOR OF CLINICAL SERVICES for Santa Barbara County Health Care Services, a progressive health care delivery organization. A fulltime position. Board certification in Internal Medicine or Family Practice. Duties include supervision and staffing of county clinics throughout Santa Barbara County. Physician will also be responsible for Ouality Care Assurance and on-going CME Programs. Competitive salary. Send CV and 3 letters of reference to Robert D. Marvan, MD, Director of Clinical Services, Santa Barbara County Health Care Services, 300 San Antonio Road, Santa Barbara, CA 93110. Phone (805) 967-2311, ext. 240.

SAN FRANCISCO KAISER-PERMANENTE MEDICAL CENTER. Full-Time Temporary Internist needed immediately for General Medical duties. Call collect—Dr. Fessell, (415) 929-4740.

CALIFORNIA: Faculty member for Family Practice Residency Program located in Orange County. Prefer Residency trained, Board Certified Family Physician. Practice and/or teaching experience preferred. Responsibilities include In-Patient coordination of Residency Program or Out-Patient teaching activities. Salary negotiable. Program affiliated with University of Southern California, School of Medicine. Send all inquiries and CV to: Raymond Jones, MD, Chairman, Search Committee, 1200 North Tustin Ave., Suite 260, Santa Ana, CA 92705. Phone: (714) 547-5404.

NEONATOLOGIST OPPORTUNITIES/ CALIFORNIA

Neonatologist board eligible or certified to join Level II Intensive Neonatal Care Unit with 10 licensed beds, 2,400 deliveries, neonatal transports, full nursing and neonatal respiratory therapy staff.

Send résumé to:

NALINI BRAHMBHATT, MD
Director of Neonatology Dept.
Centinela Hospital Medical Center
555 East Hardy Street
Inglewood, California 90307

Equal Opportunity Employer

PHYSICIANS WANTED

STUDENT HEALTH PHYSICIAN—San Jose State University 12 hours per week/10 month position, $1,316/month. Specializing in orthopedic medicine. Must be Board certified orthopedist by California Board of Medical Quality Assurance. Send rèsumé to R. C. Miller, MD, Director, Student Health Service, San Jose State University, San Jose, CA 95192.

ORTHOPEDIC SURGEON—Board Certified, Orthopedic Surgeon needed at VA Medical Center, Livermore, CA. Ideal living, good climate and clean air. Malpractice Insurance not needed. Position available at present. Salary dependent upon experience and qualifications. Contact: John F. Kane, MD, Chief of Staff, VA Medical Center, Livermore, CA 94550. Tel: (415) 447-2560, ext. 204.

PHYSICIANS WANTED

STUDENT HEALTH PHYSICIAN. Beginning September 1, 1981, an opening at Humboldt State University for a physician experienced in primary care. Must be licensed to practice medicine and surgery in California. 6,500 students; 10 month (academic year) position, 40 hour week, out-patient clinic, no nights. Excellent benefits. Salary $36,430-43,880. Submit letter of application, vitae, three letters of reference and a statement of philosophy of student health care to: J. A. Corbett, MD, Director Student Health, Humboldt State University, Arcata, CA 95521, or for more information call (707) 826-3146. Application deadline July 1, 1981.

GROW WITH US IN SUNNY ARIZONA—The INA Healthplan needs physicians in family practice and most specialties in Tucson and Phoenix. Attractive salaries and comprehensive benefits including a professional development program, retirement plan, and group incentive bonus are provided. If team interaction and casual living appeal to you, send your CV to: Professional Relations, INA Healthplan, Inc., 6115 North 7th Street, Phoenix, AZ 85014.

BOARD CERTIFIED OR ELIGIBLE FAMILY PRACTITIONER needed to start a solo practice in rapidly expanding area of Los Angeles County. Many start-up costs forgiven; the remainder are provided at lower than market rates and with delayed and prolonged pay-back schedules. Position available July 1, 1981. Send CV to National Medical Systems, Inc., 8383 Wilshire Blvd., Suite 548, Beverly Hills, CA 90211.

PART-TIME, or full-time general internal medicine doctor needed at Lake Tahoe. Contact Lakeview Medical, P.O. Box 3189, Incline Village, NV 89450.

GP OR FP PHYSICIAN. Association with well established practitioner in small community in North Central Idaho. Associate of seven years leaving in June netted between 80-90 thousand. Write to Kamiah Community Medical Clinic, Box 667, Kamiah, ID 83536.

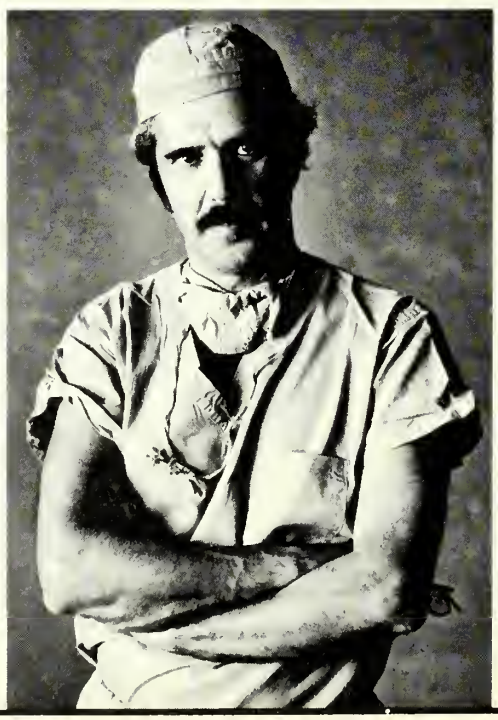
(Continued on Page 38)

We've taken the pain out of establishing your practice.

As a physician you're familiar with ways to alleviate pain. But chances are, your extensive educational process has not prepared you to handle the problems of selecting a location and establishing a successful private practice. National Medical Enterprises' Professional Relations Department has a staff of highly trained people who can help take the anguish out of making this important decision.

If you are familiar with NME you know us as one of America's largest and fastest growing health care companies that owns, operates, and manages acute care facilities that meet or exceed JCAH standards.

NME can provide Board Eligible/Board Certified physicians with private practice opportunities from Seattle, Washington to St. Petersburg, Florida - opportunities that enable you to concentrate on medicine while we assist you through the start-up phase of your new practice.



NME can offer you some of the best equipped health care facilities in the nation along with modern offices, a diverse choice of climates and a community ideally suited to your lifestyle.

Let us take the pain out of establishing a practice for you. Write and send us your curriculum vitae. Let us know your interests and where you want to live and practice. For additional information, contact:

Raymond C. Pruitt
Director, Physician Relations
National Medical Enterprises
11620 Wilshire Blvd.
Los Angeles, California 90025
(213) 479-5526
1-800-421-7470

nme NATIONAL MEDICAL ENTERPRISES, INC.

"The total health care company."

RIMSO®-50
(dimethyl sulfoxide)
50% w/w aqueous solution

INDICATIONS AND USAGE

RIMSO® - 50 (dimethyl sulfoxide) is indicated for the symptomatic relief of patients with interstitial cystitis. RIMSO® - 50 has not been approved as being safe and effective for any other indication. There is no clinical evidence of effectiveness of dimethyl sulfoxide in the treatment of bacterial infections of the urinary tract.

CONTRAINDICATIONS

None known.

WARNINGS

Dimethyl sulfoxide can initiate the liberation of histamine and there has been occasional hypersensitivity reaction with topical administration of dimethyl sulfoxide. This hypersensitivity has been reported in one patient receiving intravesical RIMSO® - 50. The physican should be cognizant of this possibility in prescribing RIMSO® - 50. If anaphylactoid symptoms develop, appropriate therapy should be instituted.

PRECAUTIONS

Changes in the refractive index and lens opacities have been seen in monkeys, dogs and rabbits given high doses of dimethyl sulfoxide chronically. Since lens changes were noted in animals, full eye evaluations, including slit lamp examinations are recommended prior to and periodically during treatment. Approximately every six months patients receiving dimethyl sulfoxide should have a biochemical screening, particularly liver and renal function tests, and complete blood count.

Intravesical instillation of RIMSO® - 50 may be harmful to patients with urinary tract malignancy because of dimethyl sulfoxide-induced vasodilation.

Some data indicate that dimethyl sulfoxide potentiates other concomitantly administered medications.

Pregnancy Category C. Dimethyl sulfoxide caused teratogenic responses in hamsters, rats and mice when administered intraperitoneally at high doses (2.5-12 gm/kg). Oral or topical doses of dimethyl sulfoxide did not cause problems of reproduction in rats, mice and hamsters. Topical doses (5 gm/kg first two days, then 2.5 gm/kg - last eight days) produced terata in rabbits, but in another study, topical doses of 1.1 gm/kg days 3 through 16 of gestation failed to produce any abnormalities. There are no adequate and well controlled studies in pregnant women. Dimethyl sulfoxide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when dimethyl sulfoxide is administered to a nursing woman.

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

A garlic-like taste may be noted by the patient within a few minutes after instillation of RIMSO® - 50 (dimethyl sulfoxide). This taste may last several hours and because of the presence of metabolites, an odor on the breath and skin may remain for 72 hours.

Transient chemical cystitis has been noted following instillation of dimethyl sulfoxide.

The patient may experience moderately severe discomfort on administration. Usually this becomes less prominent with repeated administration.

DOSAGE AND ADMINISTRATION

Instillation of 50 ml of RIMSO® - 50 (dimethyl sulfoxide) directly into the bladder may be accomplished by catheter or asepto syringe and allowed to remain for 15 minutes. Application of an analgesic lubricant gel such as lidocaine jelly to the uretha is suggested prior to insertion of the catheter to avoid spasm. The medication is expelled by spontaneous voiding. It is recommended that the treatment be repeated every two weeks until maximum symptomatic relief is obtained. Thereafter, time intervals between therapy may be increased appropriately.

Administration of oral analgesic medication or suppositories containing belladonna and opium prior to the instillation of RIMSO® - 50 can reduce bladder spasm.

In patients with severe interstitial cystitis with very sensitive bladders, the initial treatment, and possibly the second and third (depending on patient response) should be done under anesthesia. (Saddle block has been suggested).

HOW SUPPLIED

Bottles contain 50 ml of sterile and pyrogen-free RIMSO® - 50 (50% w/w dimethyl sulfoxide aqueous solution)
Dimethyl sulfoxide is clear and colorless
Protect from strong light
Store at room temperature (50° to 86°F) (15° to 30°C)
Do not autoclave
NDC # 0433-0433-05

DMSO / RIMSO / DMSO
DMSO / RIMSO / DMSO
DMSO / RIMSO / DMSO
DMSO / RIMSO / DMSO
DMSO / RIMSO / DMSO
DMSO / RIMSO / DMSO
DMSO / RIMSO / DMSO
DMSO / RIMSO / DMSO
DMSO / RIMSO / DMSO
DMSO / RIMSO / DMSO
DMSO / RIMSO / DMSO
DMSO / RIMSO / DMSO
DMSO / RIMSO / DMSO
DMSO / RIMSO / DMSO
DMSO / RIMSO / DMSO
DMSO / RIMSO / DMSO
DMSO / RIMSO / DMSO
DMSO / RIMSO / DMSO
DMSO / RIMSO / DMSO
DMSO / RIMSO / DMSO

RIMSO®-50
dimethyl sulfoxide
50% w/w aqueous solution

STERILE AND PYROGEN-FREE

50 ml

NDC #0433-0433-05

TOLL FREE ORDER NUMBER (800) 453-8432

RESEARCH INDUSTRIES CORPORATION
Pharmaceutical Division
1847 West 2300 South
Salt Lake City, Utah 84119

1981 Symposium on Obesity and the Cardiovascular Diseases

5th Annual Education Conference of the Pritikin Research Foundation: "Management of Cardiovascular Disease and Obesity Through Diet and Exercise."

October 23 and 24, 1981
Miramar-Sheraton
and
Pritikin Longevity Center
Santa Monica, California

Featured Speakers:
John W. Farquhar, M.D. Professor of Medicine, School of Medicine, Stanford Medical School. **Don C. Wukasch, M.D.** DCW, Cardiovascular surgeon and Consultant, Houstonian Preventive Medicine Center. **Norman Cousins** Adjunct Professor, UCLA School of Medicine, Former Editor, *Saturday Review*. **Nathan Pritikin** Founder and Director, Pritikin Longevity Center.

This course meets the criteria for approved Continuing Medical Education Credit for relicensure for physicians by the board of Medical Quality Assurance. (10 hours) Also approved for 10 hrs. of Continuing Education Dental Education Credit for FAGD and MAGD. Approved by the California Board Registered Nursing BRN Provider #03542 for 10 contact hours.

Fees: Physicians and Dentists: $175. (Includes banquet, meals, seminars, and abstracts) Allied Health Professionals: $95. (Includes banquet, meals and seminars)

Register early to insure reservations—Attendance is limited.

Name_____

Profession _____

Specialty _____

Address_____

_____

Telephone ( ) _____

☐ Check if you need hotel accommodations information.

Make checks payable to: Pritikin Research Foundation
For further information contact:
W Keller, Pritikin Research Foundation
1910 Ocean Front Walk, Santa Monica, Calif. 90405
(213) 450-5433, Conference Desk

(Continued from Page 36)

PHYSICIANS WANTED

EMERGENCY MEDICINE OPPORTUNITIES, full and part-time, in the Rocky Mountain states for career oriented emergency physicians. Excellent compensation and paid professional liability insurance. Send credentials to Mr. William Salmo, Chase Stone Center, Holly Sugar Building, Suite 440, Colorado Springs, CO 80903. Or call toll-free 1 (800) 525-3681 (in Colorado call collect (303) 471-4981).

GENERAL SURGEON: Bd elg./cert. needed by 8-man multispecialty Group in King City, Monterey County, California, "Steinbeck Country." King City is 1 hr. from Monterey Peninsula and 3 hrs. from San Francisco. Excellent fringe benefits, opportunity to join Corp. after 6-12 months. Send CV or contact: Allan L. Fisher, MD, or Lee S. Roberts, Administrator, at Southern Monterey County Medical Group (A professional Corporation), 210 Canal St., King City, CA 93930, (408) 385-5471.

IDAHO—FAMILY PRACTICE. Three Physician Clinic, Opening 6/1/81, University Community, Salary Negotiable, Contact D. E. Adams, MD, Moscow Clinic, P.A., Moscow, ID 83843. Tel. (208) 882-7565.

INTERNIST, CARDIOLOGIST, PULMONARY. No state income tax. Year round pleasant living. Equal opportunity employer. Send CV to R. J. Hudson, MD, Chief of Staff, Veterans Administration Medical Center, Marlin, TX 76661.

PRIMARY CARE PHYSICIAN (internist, family practitioner, or pediatrician, Board eligibility/certification) to provide outpatient care to youths of the California Youth Authority in Sacramento-Stockton area. Must also be interested in developing medical program. Excellent benefits. Salary $3,364-$4,832 per month. Contact California Youth Authority, Personnel Management Division, 4241 Williamsbourgh Dr., Sacramento, CA 95823; Telephone: (916) 445-0390.

UNIVERSITY OF OREGON, STUDENT HEALTH URGENT CARE CLINIC. Physician needed to provide urgent medical care to a student population of 17,000. Nine-month (academic year) position is available September 15, 1981. Hours negotiable, competitive salary, liberal fringe benefits. Emergency room experience desirable. Oregon license/DEA registration required. Closing date July 1981. Send vita to James K. Jackson, MD, Director, Student Health Center, University of Oregon, Eugene, OR 97403. An equal opportunity-affirmative action employer.

PACIFIC NORTHWEST—Family Practitioners-4, Cardiologist, ENT Specialists-2, General Surgeon, Internists-3, Rheumatologist, Surgeon specializing in cancer surgery, Urologists-2. Clinic adjacent to modern 150 bed hospital, serving an expanding community of approximately 50,000 people. Relaxing life style, no smog or traffic congestion. Initial investment flexible. Excellent for outdoor recreation, beaches. Two major metropolitan areas, International Airports within a couple of hours freeway drive. Enclose curriculum vita with initial response. P.O. Box 574, Chehalis, WA 98532.

DISTRICT HEALTH OFFICER, PUBLIC HEALTH—Physician experienced in Public Health and Preventive Medical Programs: to direct and provide Patient Care in Primary Care, Venereal Disease, Family Planning, Child Health, Hypertension and related preventive medical clinics in Northern Santa Barbara County. Send résumé to Robert D. Marvan MD, 300 San Antonio Rd, Santa Barbara, CA 93110.

KING CITY, MONTEREY COUNTY, CALIFORNIA: "STEINBECK COUNTRY"—8-man multispecialty group is looking for 2 Family Practitioners-FP's must be willing to take OB's. Ability to speak Spanish helpful but not mandatory. King City is located 1 hr. from Monterey Peninsula and 3 hrs. from San Francisco. Excellent fringe benefits, 1st year guaranteed minimum salary, opportunity to join corporation after 6-12 months. Send CV or contact: Allan L. Fisher, MD, or Lee S. Roberts, Admin. SoMoCo Medical Group, 210 Canal St., King City, CA 93930, or telephone (408) 385-5471.

DEVELOPMENTAL DISABILITIES PROGRAMS

Opportunities are available for internists, family practitioners and psychiatrists to work with developmentally disabled people in State residential communities. Locations from Los Angeles to northern California. Challenging and varied cases, congenial professional environment, excellent civil service benefits.

Hospital Recruitment Program
Dept. of Developmental Services
714 P Street
Sacramento, CA 95814
(916) 322-1221 collect

FINANCIAL REWARDS and PROFESSIONAL SATISFACTION . . . . . plus a whole lot more, Doctor!

We offer physician salaries in all specialties including General Practitioner and Family Practitioner that are among the highest paid in the nation and our benefit package (Including malpractice insurance) is unexcelled.

Our quality of care is excellent; our medical facilities are attractive and efficient; and our climate for both living and working is outstanding.

We are one of the largest Federally-approved HMO's in the U.S., and we currently have a few very desirable positions available in the Los Angeles area. If you are interested, please call or write:

INA HEALTH PLAN OF CALIFORNIA
1880 Century Park East
Los Angeles, CA 90067
Phone (213) 553-6677, Extension 364
Attn.: Mr. Yoakam
Director of Physician Services

ORTHOPEDIC SURGERY
OB/GYN
OTOLARYNGOLOGY
GENERAL SURGERY

We have immediate need of physicians in these and other disciplines to join us at INA/Ross-Loos Healthplan, now marking a half-century of service to Southern California members.

INA/Ross-Loos health centers are located throughout the region providing comprehensive care through utilization of community hospitals.

We offer the board eligible/certified physician an opportunity to grow with us in an environment of challenge, freedom from malpractice premiums, minimized paperwork and excellent fringe benefits.

Our compensation is highly competitive. Request details by phone or letter to:

ROSS LOOS MEDICAL GROUP, INC

ALLAN S. MIRKEN, MD
Director of Medical Personnel
INA/Ross-Loos Medical Center
1711 West Temple Street
Los Angeles, CA 90026
(213) 413-1313

PHYSICIANS WANTED

RADIOLOGIST: Board certified, experienced all major modalities plus board eligible and/or certified in nuclear medicine or equivalent, join group in hospital practice Southern California. Full curriculum citae initial reply, Box 6177, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

SITUATIONS WANTED

GENERAL SURGEON University trained, Board Certified. FACS, licensed in California, Washington State, Illinois. Prefer Trauma and Critical Care management type practice. Résumé available. Reply, Box 6209, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

FAMILY PRACTITIONER board qualified. Licensed California, Oregon, Washington, Minnesota. Age 47. Interested in all opportunities, prefer group practice, ER work, Industrial medicine, metropolitan or rural practice. Full or part time. Contact Robert L. Stein, MD, 1215 First Ave., No. Sauk Rapids, MI 56379. Tel (612) 255-0467.

OPTICIAN: California Registered Optical Dispenser desires to relocate dispensary and finishing lab near 2 or more non-dispensing Ophthalmologists. Southern Calif. area preferred but not a necessity. Box 6190, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PHYSICIAN'S ASSISTANT, 27, certified nationally in primary care and surgery, ACLS, graduate of postgraduate surgical internship, and fully trained in cardiothoracic surgery at major university hospital, seeks private or institutional affiliation. Geographic preference in sunbelt. Available July 1981. Contact John Lee, 3450-13D Wayne Ave., Bronx, NY 10467.

RADIOLOGIST BOARD CERTIFIED. Experienced in radiology and ultrasound, seeks position in Sacramento to Truckee area or available for locum tenens in August. Jack Scott, MD, 10823 Willow Valley Rd., Nevada City, CA 95959; phone (916) 265-4721.

INTERNIST 34, ABIM certified, ICU fellowship, interest and training in cardiology, University trained, excellent references, prefer California coast or foothills. Box 6206, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

RADIOLOGIST age 42, seeks position as Chief of Radiology in a medium size nonprofit California Hospital. Three years administrative experience. Can come solo or can form new group. Box 6207, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

LOCUM TENENS SERVICE
WESTERN PHYSICIANS REGISTRY

. . . offers coverage for vacation or continuing education. To participate as temporary physician or to arrange coverage for your practice, contact: **Carol Sweig, Director, 1124 Ballena Bl., Alameda, CA 94501. (415) 521-4110.**

OFFICES FOR RENT

CENTRAL CALIFORNIA—Visalia—Excellent medical city. New building in medical complex with two 1,050 sq. ft. suites available. Area needs ENT, neurosurgeon or plastic surgeon. Mill Creek Associates, 2918 W. Main, Visalia, CA 93291; (209) 733-1600.

PLEASANTON, CALIFORNIA—A very attractive office in a multi-specialty medical/dental building. Ideally located in the growing community of Pleasanton. Area especially needs Internist, ENT, Orthopedist, Endodontist and Orthodonist. Ready for occupancy, for information call Joanie Wagner, (415) 846-3288.

MEDICAL SPACE FOR LEASE
725, 975, or 1,700 sq. ft.
Blossom Hill area—So. San Jose
MAR-LO Investments • (408) 727-1979

MEDICAL SPACE TO SHARE

RENTAL (OFFICE): South Orange County, California. Sub specialized or gen. surgeon or GP to pro rata share 1,520 sq. ft. new modern, fully equipped medical suite, in large hosp. complex. Ideally loc. adj. all maj. hosp., recreation, countryside. Please call and send CV with photo to: Robert L. Epps, MD, 23961 Calle de la Magdalena, #300, Laguna Hills, CA 92653. Telephone (714) 770-6679.

MEDICAL EQUIPMENT FOR SALE

WORKING OFFICE SUPPLIES for immediate sale (repidly growing area). Could start practice immediately on site. Beautiful Puget Sound Area—Seattle Suburb. Close to skiing—Mount Rainier —University of Washington. Owner/practitioner is accepting Administrative position in distant state. Box 6168, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PRACTICES AVAILABLE

BUYING or SELLING any type Medical Practice contact California Professional Practices, 2555 Huntington Dr., Suite D, San Marino, CA 91008. (213) 796-9262 or Agent Mr. Reilly (805) 543-4782 or Cliff Rauch (714) 997-0853.

PRACTICE SALES, PLACEMENT—Orthopedics, OB/GYN, Dermatology, Internal, Family, Pediatrics, Ophthalomology, ENT, etc. Partnerships, Appraisals. Professional Practice Opportunities, 21 Altamount Dr., Orinda, CA. (415) 376-0762.

PRACTICES FOR SALE

SEATTLE—GERIATRIC PRACTICE for sale. Ideal for part-time or startup practice. Available 8/1/81. $35-45,000 net. Reply with CV to Box 6205, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

DERMATOLOGY PRACTICE. Coastal Washington. Perfect locale for outdoor sportsperson. Price negotiable. Contact: E. J. Blum, MD, 1006 N. H St., Aberdeen, WA 98520.

MEDICAL OFFICE PRACTICE. Downtown San Francisco. Write Box 6208, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

FLAGSTAFF MEDICAL BUILDING LEASE AND OWN

Located next to the Flagstaff Hospital and Medical Center on the corner of Forest and Beaver Streets. A Pharmacy, laboratory and radiology in the complex plus parking easily accessible to either your office or the hospital makes the Flagstaff Medical Building the desired choice for the largest number of practicing physicians in any medical building located in Northern Arizona. Your customized medical office suite (ranging from 800 to 2,000 sq. ft.) is now available at a most reasonable cost plus the existing partnership is now offering those tenants signing leases before May 15, 1981 the opportunity to purchase an ownership interest in the building. Please contact:

BRUCE O. UTTERBACK, CPM, FLAGGSTAFF MEDICAL BUILDING, 1355 N. BEAVER, FLAGSTAFF, ARIZONA 86001. (602) 774-4416.

PSL
PRACTICE SALES & LOCATIONS

PRACTICES FOR SALE

All specialities available. Request practice list.

NEW OFFICE SET-UPS

Locations for lease, lease w/equity, purchase.

APPRAISALS

Practice appraisal for buyouts, dissolutions, etc. Widely accepted as the most comprehensive and rational.

PRACTICE SALES & LOCATIONS, INC.
17942 Skypark Circle, Suite D
Irvine, CA 92714
(714) 641-9203

PRACTICES FOR SALE

FAMILY PRACTITIONER—35 yrs. practice in Centralia, Washington. Retiring. Contact Ross M. Galvin, MD, Telephone (206) 736-2891 or 736-3848.

LARGE RURAL PRACTICE available immediately, physician deceased. Full laboratory and x-ray. 24-bed hospital next door. 745 Main, Cedarville, CA 96104. (916) 279-6115.

LEGAL COUNSEL

BMQA
Former Deputy Atty. General representing BMQA & Dept. of Health
Now specializing in BMDA investigations and disciplinary actions. Hospital Staff Privilege cases and Defense Malpractice cases thruout Calif.
LAW OFFICES OF SAMUEL E. SPITAL, A PROFESSIONAL CORP
1200 THIRD AVE. #1200 SAN DIEGO CA 92101 (714) 231-4848

CLASSIFIED
INFORMATION
(415) 777-2000
EX 220
AND
(415) 777-0424

BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

AUTHOR'S GUIDE TO JOURNALS IN THE HEALTH FIELD—Edited by Donald B. Ardell, PhD, and John Y. James, MPH. The Haworth Press, Inc., 149 Fifth Avenue, New York City (10010), 1980. 139 pages, $16.95.

BORN AT RISK—B. D. Colen. St. Martin's Press, 175 Fifth Avenue, New York City (10010), 1981. 212 pages, $9.95.

CURRENT MEDICAL DIAGNOSIS & TREATMENT 1981—Edited by Marcus A. Krupp, MD, Clinical Professor of Medicine Emeritus, Stanford University School of Medicine; Director of Research, Palo Alto Medical Research Foundation; and Milton J. Chatton, MD, Clinical Professor of Medicine, Stanford University School of Medicine; Senior Attending Physician, Santa Clara Valley Medical Center, San Jose; Research Associate, Palo Alto Medical Research Foundation, Palo Alto, CA; With Associate Authors. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1981. 1,100 pages, $21.00.

CURRENT SURGICAL MANAGEMENT OF NEUROLOGIC DISEASE—Edited by Charles B. Wilson, MD, Professor and Chairman, Department of Neurological Surgery, University of California, San Francisco; and Julian T. Hoff, MD, Professor and Vice Chairman, Department of Neurological Surgery, University of California, San Francisco. Longman Inc., 19 West 44th Street, New York City (10036), 1980. 356 pages, $39.50.

THE EOSINOPHIL IN HEALTH AND DISEASE—Edited by Adel A. F. Mahmoud, MD, PhD, Professor of Medicine, Director, Division of Geographic Medicine, Department of Medicine, Case Western Reserve University, University Hospitals, Cleveland; and K. Frank Austen, MD, Theodore Bevier Bayles Professor of Medicine, Department of Medicine, Harvard Medical School, Chairman, Department of Rheumatology and Immunology, Brigham and Women's Hospital, Boston; Technical Editor: Arlene Stolper Simon, Department of Rheumatology and Immunology, Brigham and Women's Hospital, Boston. Grune & Stratton, Inc., 111 Fifth Avenue, New York City (10003), 1980. 364 pages, $39.50.

HAVING A BABY—Eric Trimmer, MB, BS, MRCGP. St Martin's Press, Inc., 175 Fifth Ave., New York City (10010), 1981. 142 pages, illustrated in color, $8.95 (paperback).

HOW BRAVE A NEW WORLD?—Dilemmas in Bioethics—Richard A. McCormick, SJ. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1981. 440 pages, $15.95.

INFORMATION TO AUTHORS 1980-1981—Editorial Guidelines Reproduced From 246 Medical Journals—Compiled by Harriet R. Meiss and Doris A. Jaeger, Mount Sinai School of Medicine of the City University of New York. Urban & Schwarzenberg, Medical Publishers, 7 East Redwood Street, Baltimore (21202), 1980. 665 pages, $26.00 (softbound).

INTERPRETING ECGs—An Advanced Self-Test Guide—Ali Haddad, MD, with David C. Dean, MD, Consulting Editor. Medical Economics Books, 680 Kinderkamack Road, Oradell, NJ (07649), 1981. 146 pages, illustrated, soft cover, $7.95.

NEW HOPE THROUGH HYPNOTHERAPY—The Joe Keeton Phenomenon—Monica O'Hara. Abacus Press, Abacus House, Speldhurst Road, Tunbridge Wells, Kent TN4 OHU, England. 150 pages, $13.50.

THE 1980 YEAR BOOK OF FAMILY PRACTICE—Editor: Robert E. Rakel, MD, Professor and Head, Department of Family Practice, University of Iowa College of Medicine; Associate Editors: Forrest Dean, MD; Charles E. Driscoll, MD; Charles W. Smith, MD, and James L. Wilson, MD. Year Book Medical Publishers, 35 East Wacker, Chicago, IL (60601), 1980. 453 pages, $32.95.

PEARLS IN DIAGNOSTIC RADIOLOGY—Harold D. Rosenbaum, MD, Chairman, Department of Diagnostic Radiology, University of Kentucky College of Medicine, Lexington. Longman Inc., 19 West 44th Street, New York City (10036), 1980. 240 pages, $32.50.

PEDIATRIC ENDOCRINOLOGY—S. Douglas Frasier, MD, Professor of Pediatrics and Physiology/Biophysics, University of Southern California School of Medicine, Los Angeles. Grune & Stratton, Inc., 111 Fifth Avenue, New York City (10003), 1980. 375 pages, $29.50.

THE PHYSICIAN AND THE MENTAL HEALTH OF THE CHILD—II. The Psychological Concomitants of Illness—Editors: Herbert J. Grossman, MD, and Robert L. Stubblefield, MD. Order Department OP-079, American Medical Association, P.O. Box 821, Monroe, WI (53566), 1980. 155 pages, $7.00.

PRACTICAL RHEUMATOLOGY: DIAGNOSIS AND MANAGEMENT—Rodney Bluestone, MB, FRCP, Clinical Professor of Medicine, University of California, Los Angeles; Associate Attending Physician, Cedars-Sinai Medical Center, Los Angeles. Addison-Wesley Publishing Company, Inc., Health Sciences Division, 2727 Sand Hill Road, Menlo Park, CA (94025), 1980. 239 pages, $23.95.

THE WAY OF HERBS—Michael Tierra, CA, ND. Unity Press, 235 Hoover Road, Santa Cruz, CA (95065), 1980. 216 pages, $6.95 (paperback).

STATISTICAL METHODS FOR SURVIVAL DATA ANALYSIS—Elisa T. Lee, PhD, Department of Biostatistics and Epidemiology, School of Public Health, University of Oklahoma, Oklahoma City. Lifetime Learning Publications, Ten Davis Drive, Belmont, CA (94002), 1980. 557 pages, $26.95.

this publication is available in microform

Please send me additional information.

Name _____

Institution _____

Street _____

City _____

State _____ Zip _____

University Microfilms International

300 North Zeeb Road
Dept. P.R.
Ann Arbor, MI 48106
U.S.A.

18 Bedford Row
Dept. P.R.
London, WC1R 4EJ
England

(Continued from Page 23)

November 6-8—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Sheraton, Anaheim. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

November 11—**Acid Base Disorders.** LLU. Wednesday.

November 14—**Cardiology for the Primary Care Physician.** UCD. Saturday.

November 17-20—**First Mexican-American Congress of Allergy and Clinical Immunology.** UCSD at San Diego (17-18) and Tijuana (19-20). Tuesday-Friday. 20 hrs. $175 before Sept. 15; $200, thereafter. Contact: Robert N. Hamburger, MD, Immunology and Allergy Div., UCSD (M-009D), La Jolla 92093.

December 4-5—**Management of Today's Endocrine Problems: A Medical and Surgical Update.** Scripps Clinic and Research Foundation, La Jolla. Friday-Saturday. 10 hrs. $125. Contact: Dianne Tisue, Dept. of Academic Affairs, Scripps Clinic and Research Fndn., 10666 N. Torrey Pines Rd., La Jolla 92037. (714) 455-9100.

December 4-5—**Cardiac Ischemia and Arrhythmias—Current Concepts for Diagnosis and Treatment.** International Medical Education Corp. at Islandia Hyatt, San Diego. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

December 4-6—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at MGM Grand, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

December 5-7—**Advances in Heart Disease 1982.** American College of Cardiology and UCD at Fairmont Hotel, San Francisco. Saturday-Monday. Contact: Registration Sec., Extramural Programs Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014. (301) 897-5400.

December 5-10—**American Academy of Dermatology.** San Francisco. Saturday-Thursday. Contact: Cheryl Nordstedt, Dir., Meetings and Conventions, AAD, 820 Davis St., Evanston, IL 60201. (312) 869-3954.

December 9—**Hypertension.** LLU. Wednesday. 4 hrs.

December 10-13—**Intensive Care for Neurological Trauma and Disease: Update 1981.** See Surgery, December 10-13.

OBSTETRICS AND GYNECOLOGY

July 8—**Current Concepts in Contraception.** LLU. Wednesday. 4 hrs.

August 8-15—**Reproductive Endocrinology, Infertility and Contraception.** See Of Interest To All, August 8-15.

August 29-September 5—**Concepts in Infertility.** See Of Interest To All, August 29-September 5.

October 17—**Infections and Pregnancy.** UCD and March of Dimes at Sacramento. Contact: UCD.

October 26-30—**11th Annual Review Course in Obstetrics and Gynecology.** USC at Hilton, Pasadena. Monday-Friday.

October 26-31—**Review Course in Clinical Obstetrics and Gynecology and Gynecological Histopathology.** Memorial Hospital Medical Center-UCI Center for Health Education at Sheraton, Newport Beach. Monday-Saturday. Contact: Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-2311.

November 11-13—**Perinatology.** UCSD at Holiday Inn at Embarcadero, San Diego. Wednesday-Friday.

December 5-7—**Current Issues in Perinatal Medicine.** Memorial Hospital Medical Center-UCI Center for Health Education at Rancho Las Palmas Resort, Rancho Mirage. Saturday-Monday. Contact: MHMC-UCI Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-2311.

PEDIATRICS

September 23-24—**38th Annual Brennemann Memorial Lectures.** Los Angeles Pediatric Society at Hilton, Los Angeles. Wednesday-Thursday. Contact: LAPS, P.O. Box 2022, Inglewood 90305. (213) 757-1198.

September 25-29—**Pediatric Urology.** UCD at Silverado Country Club, Napa. Friday-Tuesday.

October 2-3—**Pediatric Gastroenterology and Nutrition.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday. 10 hrs.

October 18—**The Hearing Impaired: Identification, Counseling and Rehabilitation.** Peninsula Hospital and San Mateo Co. Office of Education at Peninsula Hospital, Burlingame. Sunday. Contact: Les Demme, Peninsula Hosp. and Med. Ctr., 1783 El Camino Real, Burlingame 94040. (415) 697-4061.

December 4-6—**Kids Have Bones, Too.** UCD. Friday-Sunday.

PSYCHIATRY

June 22-26—**Comparative Psychotherapies.** USC at Hotel del Coronado, Coronado. Monday-Friday. 21½ hrs. $250.

June 24-25—**Crisis Intervention.** Dept. of Health, Health Training Center/North, Emeryville. Wednesday-Thursday. 12 hrs. Contact: Health Training Ctr., 5850 Shellmound St., Suite 390, Emeryville 94608. (415) 464-0685.

June 28-30—**Family Problems, Aging and Sexuality.** See Of Interest To All, June 28-30.

July 8-10—**Update in Psychiatry: Psychopharmacology.** UCSD at Hanalei Hotel, San Diego. Wednesday-Friday.

July 26-30—**Summer Seminar, Session II.** Mental Research Institute, Palo Alto. Sunday-Thursday. 27 hrs. $270. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

July 31-August 1—**Innovations: New Trends in Family Therapy, Brief Therapy and Family Medicine.** Mental Research Institute at Sheraton-Palace, San Francisco. Friday-Saturday. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

August 15-21—**Neuropsychiatric Issues in the Law, Education and Medicine: Hyperactivity and Dyscontrol Syndrome.** So. Calif. Neuropsychiatric Institute and Hawaii Psychiatric Society at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 15 hrs. Contact: Gail Waldron, MD, 6794 La Jolla Blvd., La Jolla 92037. (714) 454-2102.

August 20-22—**Practical Medicine for the General Psychiatrist.** UCSD at Hyatt Islandia, San Diego. Thursday-Saturday.

October 24—**Psychotherapy: Office Approach for the Primary Care Physician.** UCD. Saturday.

RADIOLOGY AND PATHOLOGY

June 16-19—**Society of Nuclear Medicine.** Hilton, Las Vegas. Tuesday-Friday. 28 hrs. $60, members; $120, nonmembers. Contact: Registrar, SNM, 475 Park Ave. S., New York 10016. (212) 889-0717.

July 18-25—**Laboratory Medicine.** USC at Kauai Surf Hotel, Kauai, Hawaii. One week. 29½ hrs. $350.

August 8-15—**Radiology.** USC at Maui Surf Hotel, Maui, Hawaii. One week. 28 hrs. $395.

August 12—**Chest Films—An Indispensable Diagnostic Tool.** LLU. Wednesday. 4 hrs.

August 16-21—**23rd Annual Postgraduate Course in Dermal Pathology.** Memorial Hospital Medical Center-UCI Center for Health Education at Newporter Inn, Newport Beach. Sunday-Friday. Contact: Program Coordinator, Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

August 29-September 5—**Diagnostic Radiology: An In-Depth Seminar Approach to Diagnostic Imaging.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 24 hrs. $345.

September 5-9—**Dermatopathology.** See Medicine, September 5-9.

September 13-17—**Digital Radiography: Clinical Applications and Technical Advances.** STAN. Sunday-Thursday.

September 19—**8th Annual Radiology Symposium.** So. Calif. Permanente Medical Group at Hilton Hotel, Los Angeles. Saturday. Contact: Felecia Madison, SCPMG, Education and Research Dept., 4747 Sunset Blvd., 4th Floor, Los Angeles 90027. (213) 667-4516.

October 2—**Uroradiology Seminar.** Orange Co. Urological Soc. and Western Section, American Urological Assn., at South Coast Plaza Hotel, Costa Mesa. Friday. $100. Contact: Kathy De Santis, Western Section, AUA, 21510 S. Main St., Carson 90745. (213) 549-3470.

October 8-9—**Fine Needle Aspiration of Breast and Thyroid.** UCSF at Sir Francis Drake Hotel, San Francisco. Thursday-Friday. 13 hrs.

October 8-10—**International Symposium on Medical Virology.** UCI at Disneyland Hotel, Anaheim. Thursday-Saturday. 23 hrs. $100, before Sept. 15; $125, thereafter. Contact: Dr. Luis M. de la Maza, Dept. of Pathology, UCI Med. Ctr., Orange 92668. (714) 634-6868.

Postgraduate Videotape Programs in Diagnostic Radiology. Developed by Dept. of Radiology, UCSF. 27 programs in all aspects of diagnostic radiology. Outstanding national and international guest lecturers in addition to UC staff present basic approaches to radiographic interpretation and technique as well as new research and clinical advances. Contact: Radiology Postgraduate Ed. Section, UCSF, Dept. of Rad., Rm. M396, San Francisco 94143. (415) 666-5731, between 7:00 a.m. and 4:00 p.m.

SURGERY

June 20-27—**Ophthalmology.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. $350.

June 26-27—**Surgery Trauma.** UCLA. Friday-Saturday.

September 9—**New Concepts in the Diagnosis and Management of Peripheral Vascular Disease.** LLU. Wednesday. 4 hrs.

September 18-19—**Ophthalmology Update.** UCD, PMC, UCSF, STAN at Sheraton-Palace, San Francisco. Friday-Saturday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062. (415) 563-4321, ext. 2761.

September 19—**Oxygen Transmission and Extended Wear Contact Lenses.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024.

September 25-29—**Pediatric Urology.** See Pediatrics, September 25-29.

October 2—**Uroradiology Seminar.** See Radiology and Pathology, October 2.

October 2-3—**Cataract Surgery and Intraocular Lenses Course.** Jules Stein Eye Institute, Los Angeles. Friday-Saturday. 16 hrs. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024.

October 3-10—**Introductory Seminar on Operative Arthroscopy.** UCLA at Maui. One week.

October 11-16—**American College of Surgeons—67th Annual Clinical Congress.** Fairmont and Hilton Hotels, San Francisco. Sunday-Friday. Contact: Fred C. Spillman, Convention Mgr., ACS, 55 E. Erie St., Chicago 60611. (312) 664-4050.

October 15-17—**Hip Replacement.** UCLA. Thursday-Saturday.

October 16-17—**Fracture Bracing Workshops.** USC at University Hilton, Los Angeles. Friday-Saturday. 17 hrs. $375.

November 11-15—**Pediatric Surgery of the Head and Neck: A Frontier Symposium.** Institute for Medical Education and Research and UCSD at Silverado Country Club, Napa. Wednesday-Sunday. 20 hrs. Contact: Inst. for Med. Ed. and Research, 135 Dickinson St., San Diego 92103. (714) 272-3126.

November 12-14—**Techniques in Urinary Tract Surgery.** American Urological Assn. at Fairmont Hotel, San Francisco. Thursday-Saturday. 16 hrs. Contact: Office of Education, AUA, P.O. Box 1129, Aspen, CO 81611.

December 2-4—**Corneal and Refractive Surgery—An Up-to-Date Evaluation.** UCSF. Wednesday-Friday.

December 4-5—**Management of Today's Endocrine Problems: A Medical and Surgical Update.** See Medicine, December 4-5.

December 5—**The Management of Thyroid Eye Disease.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024.

December 9-11—**Arthroscopic Surgery 1981.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. Contact: MHMC-UCI Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-2311.

December 10-13—**Intensive Care for Neurological Trauma and Disease: Update 1981.** Comprehensive Central Nervous System Injury Fndn. and Institute for Medical Education and Research at Mission Bay Hilton, San Diego. Thursday-Sunday. 20 hrs. $250. Contact: Comprehensive CNS Injury Fndn., P.O. Box 9494, San Diego 92109.

December 11-12—**Ophthalmology Update.** UCD, PMC, UCSF, STAN at Sheraton-Palace, San Francisco. Friday-Saturday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062. (415) 563-4321, ext. 2761.

OF INTEREST TO ALL PHYSICIANS

June 26—**Occupational Safety and Health for Hospitals: Keeping a Safe and Healthy Workplace.** PMC. Friday. 6 hrs. $50.

June 28-30—**Family Problems, Aging and Sexuality.** USC. Sunday-Tuesday. 17¼ hrs. $136.

August 1—**Herpes.** UCLA at Memorial Hospital, Long Beach. Saturday.

August 8-15—**Reproductive Endocrinology, Infertility and Contraception—3rd Annual Course.** USC at Royal Lahaina Hotel, Maui, Hawaii. One week. 21½ hrs. $325.

August 15-26—**24th Annual Postgraduate Refresher Course.** USC at Honolulu and Maui. 12 days. 37 hrs. $375.

August 16-21—**9th Annual Family Practice Refresher Course.** UCD at Hyatt Del Monte, Monterey. Sunday-Friday. 36 hrs.

August 29—**The Medical Applications of Exercise.** UCD at El Rancho Racquet Club, Sacramento. Saturday.

August 29-30—**Hemodynamic Monitoring—Pulmonary Artery Catheterization.** Calif. Society of Anesthesiologists at Stanford Univ. Medical Center. Saturday-Sunday. 15 hrs. $275, CSA members; $325, nonmembers. Contact: Richard Manley, CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

August 29-September 5—**Concepts in Infertility—1981—Fifth Annual Edward Tyler Symposium.** Tyler Medical Clinic and Univ. of Hawaii School of Medicine at Royal Lahaina Hotel, Maui, Hawaii. One week. Contact: Frank De Llyls, Astra Tours and Travel, 10929 Weyburn Ave., Los Angeles 90024. (213) 479-4444.

August 30-31—**Orthopedics for the Primary Care Physician.** UCLA at Newporter Inn, Newport Beach. Sunday-Monday.

September 7-18—**Intensive Residency in Occupational Medicine, Session III.** UCSF. Two weeks.

September 19-20—**Eating Disorders.** UCLA. Saturday-Sunday.

September 21-23—**Spectrum of Recovery: From Conception Through the Golden Years.** Scripps Memorial Hospital, Alcoholism Treatment Center, at Islandia Hyatt, San Diego. Monday-Wednesday. 15 hrs. $190. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (714) 453-6222.

September 21-24—**American Academy of Family Physicians.** Convention Center, Las Vegas. Monday-Thursday. 30+

hrs. Contact: Edward E. Daleske, Sec., Committee on Scientific Programs, AAFP, 1740 W. 92nd St., Kansas City, MO 64114. (816) 333-9700.

October 12-14—**Interpretative Enzymology.** UCSD at Sheraton Airport Hotel, San Diego. Monday-Wednesday.

October 12-16—**Clinical Update.** American Medical Assn. at Ilikai Hotel, Honolulu. Monday-Friday. Contact: Dept. of Meeting Services, AMA, 535 N. Dearborn St., Chicago 60610. (312) 751-6000.

October 12-16—**Hawaii Medical Association—Annual Meeting.** Ilikai Hotel, Honolulu. Monday-Friday. Contact: HMA, 320 Ward Ave., Honolulu 96814. (808) 536-7702.

October 14-15—**Alcoholism and the Family.** PMC at Sheraton at Fisherman's Wharf, San Francisco. Wednesday-Thursday. 12 hrs. $85.

October 18-21—**Sports Medicine Today.** UCD at Stanford Sierra Lodge, Fallen Leaf Lake. Sunday-Wednesday.

October 18-23—**Recognition and Management of Diving Casualties.** UCSD at Travelodge, Harbor Island, San Diego. Sunday-Friday.

October 24—**Psychotherapy: Office Approach for the Primary Care Physician.** UCD. Saturday.

October 28-30—**Workshops in Clinical Hypnosis.** USCD at Village Inn, La Jolla. Wednesday-Friday.

November 1-6—**American Congress of Rehabilitation Medicine and American Academy of Physical Medicine and Rehabilitation.** Town and Country, San Diego. Sunday-Friday. Contact: Creston C. Herold, Exec. Dir., 30 N. Michigan Ave., Suite 922, Chicago 60602. (312) 236-9512.

November 2-6—**Postgraduate Institute for Primary Care Physicians—Symposium on Inpatient Care.** UCSD at Islandia Hyatt, San Diego. Monday-Friday.

November 2-6—**Intensive Care.** STAN. Monday-Friday. 25 hrs. $325.

Needs Identification and Fulfillment Tailored to the Individual (NIFTI). UCSF. A new contemporary approach to formal continuing medical education. Participating physicians identify their own CME needs which will be met by a program specifically tailored by UCSF faculty for each individual physician. 25 hrs. minimum; 100, maximum. Fee: $350; $200, UCSF alumni. Contact: Extended Programs in Medical Education, 569-U, Univ. of Calif., San Francisco 94143. (415) 666-4251.

Audio-Digest Foundation—A nonprofit subsidiary of CMA. Provides by subscription twice-a-month tape recorded summaries of leading national meetings and authoritative surveys of current literature. A catalog of lectures and panel discussions in all areas of medical practice is also available. Contact: Audio-Digest Foundation, 1577 E. Chevy Chase Dr., Glendale 91206.

Videotape Postgraduate Course for the Primary Care Physician. UCSF, School of Medicine, Div. of Ambulatory and Community Medicine. 24 Category I hrs. upon completion of course as designed—12 programs each year. Contact: Ms. Estelle Nelson, UCSF, Rm. 432-A, 400 Parnassus Ave., San Francisco 94143. (415) 666-1445.

ALASKA, MONTANA and IDAHO

This list of continuing education programs in Alaska, Montana and Idaho is supplied by the University of Washington School of Medicine's program of regional medical education in Washington, Alaska, Montana and Idaho (WAMI). To have events listed, please send information to: WAMI Program, CME Calendar, D-207 Health Sciences Building, School of Medicine, SC-64, University of Washington, Seattle, Washington 98195; or phone (206) 543-6995.

ALASKA

June 18—Consultation on Adolescent Problems/Systems Approach—Univ. of Wash. Psychiatry Sessions (Anchorage). Thursday, 7:30 pm-9:30 pm. Alaska Psychiatric Institute Medical Library. Contact: John Wreggit, MD, 511 East 45th, Anchorage, AK 99503. (907) 274-7579.

MONTANA

No courses scheduled.

IDAHO

No courses scheduled.

NEW MEXICO

All courses listed below have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. The Continuing Medical Education Committee of the New Mexico Medical Society has certified all courses listed below as meeting the criteria for Category 4 under the New Mexico Board of Medical Examiners Continuing Medical Education regulations.

Information and requests for accreditation should be sent to the chairman of the CME Committee, New Mexico Medical Society, P.O. Box 9366, Albuquerque, NM 87119 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 247-0539.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

June 25-27—**Oxygen Transport to Human Tissues—A Symposium in Honor of Dr. U. C. Luft.** Albuquerque. Thursday-Saturday. Lovelace Medical Center. 16.5 credit hours. Contact: Waneta C. Tuttle, PhD, Lovelace Medical Foundation, 5400 Gibson SE, Albuquerque, NM 87108. (505) 832-7155.

July 20-23—**Ruidoso Family Practice Seminar.** Ruidoso. Monday-Thursday. Inn of the Mountain Gods. 18 credit hours, also AAFP Prescribed. Contact: Convention Director, PO Box 456, Sunland Park, NM 88063. (505) 247-0539.

July 22-25—**Current Concepts in the Surgical Pathology of the Thyroid, Parathyroid, Thymus and Mediastinum.** Santa Fe. Wednesday-Saturday. Santa Fe Hilton. 14 credit hours. Contact: Symposia de Santa Fe, PO Box 5175, Santa Fe, NM 87502. (505) 982-1911.

August 5-8—**Radiology for FP's—An Update.** Santa Fe. Wednesday-Saturday. Santa Fe Hilton Inn. 16 credit hours, also AAFP Prescribed. Contact: W. J. Levy, MD, Symposia de Santa Fe, PO Box 5175, Santa Fe, NM 87502. (505) 982-1911.

September 3-5—**Sports Medicine.** Albuquerque. Thursday-Saturday. Location to be announced. 10 credit hours. Contact: Otto Appenzeller, MD, Dept. of Neurology, UNM School of Medicine, Albuquerque, NM 87131. (505) 277-3342.

September 27-October 1—**Southwest Obstetrical & Gynecological Society 1981 Annual Meeting.** Santa Fe. Sunday-Thursday. Inn at Loretto. 30 credit hours, also AAFP Prescribed. Contact: W. Duane McCarty, MD, 5400 Gibson SE, Albuquerque, NM 87108. (505) 842-7291.

OREGON

This bulletin of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

Emanuel Hospital, 2801 N. Gantenbein Street, Portland 97227:

Every Friday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Contact: Philipa McClure, Emanuel Hospital, 2801 N. Gantenbein St., Portland, OR 92227. (503) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, OR 97213. (503) 234-8211.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00-9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee, P.O. Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

University of Oregon Medical School, Department of Psychiatry, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, University of Oregon Medical School. Contact: Dept. of Psychiatry, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8144.

University of Oregon Medical School, Department of Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, University of Oregon Medical School. Contact: Dept. of Medicine, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8607.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center, Portland. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-7590.

OBSTETRICS AND GYNECOLOGY

October 1-3—**Fifth Annual Pacific NW Review of Obstetrics & Gynecology.** Thursday-Saturday. Thunderbird-Jantzen Beach, Portland, Oregon. For additional information please contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, Portland, OR 97201. (503) 225-8700.

OPHTHALMOLOGY

October 1-2—**Vitrectomy.** Thursday-Saturday. University of Oregon Health Sciences Center, Portland. For additional information please contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, Portland, OR 97201. (503) 225-8700.

SURGERY

July 23-25—**Plastic Surgery for the General Surgeon.** Thursday-Friday. Thunderbird at Jantzen Beach, Portland. For additional information please contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, Portland, OR 97201. (503) 225-8700.

November 20—**Soft Tissue Surgery Techniques.** Friday. University of Oregon Health Sciences Center, Portland. For additional information please contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, Portland, OR 97201. (503) 225-8700.

INTEREST TO ALL PHYSICIANS

September 11-12—**Gastroenterology: Current Concepts in Colon Disorders, Hepatitis and Obstructive Jaundice.** Friday-Saturday. Ashland Hills Inn, Ashland, Oregon. For additional information please contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, Portland, OR 97201. (503) 225-8700.

September 25—**Second Annual Poisoning & Toxicological Emergencies Conference.** Friday. Red Lion at Jantzen Beach, Portland. For additional information please contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, Portland, OR 97201. (503) 225-8700.

November 12-13—**Symposium on Critical Care Medicine.** Thursday-Friday. Red Lion at Jantzen Beach, Portland. For additional information please contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, Portland, OR 97201. (503) 225-8700.

December 4-5—**Urology for the Non-Urologist.** Friday-Saturday. Red Lion-Downtown, Portland. For additional information please contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, Portland OR 97201. (503) 225-8700.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. Please send information to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle 98121; or phone (206) 623-4801.

June 15-19—**Death Investigation.** Seattle. Monday-Friday. Contact: U/W School of Medicine.

COURSE SPONSORS AND CONTACT INFORMATION

CME PIERCE COUNTY—Contact: Mrs. Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON) — Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Sandra McDonald, Division of Continuing Medical Education, Virginia Mason Medical Center, 1100 Ninth Avenue, Seattle, WA 98101. (206) 223-6898.

June 16—**Antibiotic Update.** U/W Health Sciences Building. Seattle. Tuesday. Contact: U/W School of Medicine.

June 18-19—**Respiratory Care.** Seattle. Thursday-Friday. Contact: U/W School of Medicine.

June 18-20—**Modern Office Procedures: Minor Surgeries.** Seattle. Thursday-Saturday. Contact: U/W School of Medicine.

June 22—**Ophthalmology for the Internist—Univ. of Wash. Internal Medicine Review Sessions** (Wenatchee). Monday. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

July 19-27—**Alaska Cruise: OB/GYN.** Sunday-Monday. Contact: U/W School of Medicine.

July 24-26—**Washington State Society of Anesthesiologists: Seafair III Anesthesia Meeting.** Seattle. Friday-Sunday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

July 27-31—**Psychiatry & The Behavioral Sciences: The 1980s.** Bayshore Inn. Vancouver, British Columbia. Monday-Wednesday and Friday. Contact: U/W School of Medicine.

August 5-7—**Great Debates in Otolaryngology.** Seattle. Wednesday-Friday. Contact: U/W School of Medicine.

August 21-28—**Alaska Cruise: Radiology.** Friday-Friday. Contact: U/W School of Medicine.

August 21-28—**Alaska Cruise: Strabismus.** Friday-Friday. Contact: U/W School of Medicine.

September 18—**Progress in Breast Cancer.** Seattle. Friday. Providence Medical Center. Contact: Evelyn Foote, Physician Education, Providence Medical Center, 500 17th Avenue C-34008, Seattle, WA 98124. (206) 326-5555.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the Academy for Continuing Medical Education, a foundation of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Academy for Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the Academy at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the Academy for current details.

GRAND ROUNDS

SPONSOR: Primary Children's Medical Center
TITLE: **Pediatric Grand Rounds**
LOCATION: PCMC
DATE: First and third Thursdays—8:00 a.m.
CONTACT: Cathy Van Komen (801) 363-1221

SPONSOR: Utah Valley Hospital, Provo
TITLE: **Interdepartmental Grand Rounds**
LOCATION: UVH
CONTACT: Gary Watts, MD (801) 373-7850 (Ext. 2143)

* * *

June 17-19

SPONSOR: University of Utah
TITLE: **Society for Epidemiologic Research**
LOCATION: Snowbird
FEE: To be announced
CREDIT: 22.5 hours
CONTACT: Joseph L. Lyon, MD (801) 581-5270

June 22-25

SPONSOR: University of Utah
TITLE: **Alcoholism and Other Drug Dependencies**
LOCATION: University Medical Center, Classroom C
FEE: To be announced
CREDIT: 25 hours
CONTACT: James R. Swenson, MD (801) 581-7985

June 30-July 3

SPONSOR: University of Utah
TITLE: **8th Annual Symposium in Clinical Echocardiography: New Developments in Cardiac Ultrasound**
LOCATION: Snowbird
FEE: To be announced
CREDIT: 23.5 hours
CONTACT: A. D. Hagan, MD (801) 350-1680

July 31-August 6

SPONSOR: University of Utah
TITLE: **Radiology 3rd Annual Postgraduate Course**
LOCATION: Inside Passage, Alaska
FEE: $300.00
CREDIT: 28 hours
CONTACT: Ann Osborn, MD (801) 581-7552

September 3-5

SPONSOR: University of Utah
TITLE: **Advanced Trauma Life Support**
LOCATION: Tri-Arc Travelodge, Salt Lake City
FEE: $300.00
CREDIT: 17 hours
CONTACT: Tricia Neilson, RN (801) 533-6435

September 9-11

SPONSOR: University of Utah/Utah State Medical Association
TITLE: **Annual Scientific Session**
LOCATION: Hotel Utah, Salt Lake City
FEE: $50.00
CREDIT: 12 hours
CONTACT: Maxcine Fry (801) 355-7477

SPONSORS OF COURSES—ABBREVIATIONS

AF: Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.
CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.
CWH: Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461
FHP: Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.
HAFB: Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.
HCH: Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.
LDSH: Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.
MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.
OEH: Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.
OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409
PCMC: Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.
SHCC: Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.
SLSC: Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.
UAFP: Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.
UUMC: University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.
UVH: Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.
VAMC: Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—4107 Laurel St., Anchorage 99504. Annual Meeting: 1982—date and place to be announced.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. Annual Meeting: 1982—date and place to be announced.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: March 12-17, 1982, Disneyland Hotel, Anaheim.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. Annual Meeting: September 9-12, 1981, Keystone.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. Annual Meeting: October 12-16, 1981, Ilikai Hotel, Honolulu.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. Annual Meeting: July 23-26, 1981, Sun Valley.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Annual Meeting: October 1-3, 1981, Copper King Inn, Butte.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. Annual Meeting: 1982—date and place to be announced.

New Mexico Medical Society—2650 Yale SE, Albuquerque 87106. Annual Meeting: 1982—date and place to be announced.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. Annual Scientific Session: October 29-30, 1981, Portland.

Utah State Medical Association—540 East Fifth South, Salt Lake City 84102. Annual Meeting: September 8-11, 1981, Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. Annual Meeting: September 24-27, 1981, Davenport Hotel, Spokane.

Wyoming State Medical Society—P.O. Drawer 4009, Cheyenne 82001. Annual Meeting: June 22-26, 1981, Americana Snow King Hotel, Jackson.

October 9

SPONSOR: University of Utah
TITLE: **Regional Joint ACP-ASIM Meeting Topics in Pharmacology**
LOCATION: Salt Lake Hilton
FEE: $20.00
CREDIT: To be announced
CONTACT: Gregory A. Schwitzer, MD (801) 581-7818

October 16-27

SPONSOR: Washington University School of Medicine/ Utah State Medical Association
TITLE: **Western Mediterranean Air/Sea Cruise and Medical Seminar**
LOCATION: Portugal, Morocco, Gilbraltar, Spain, Italy, France
FEE: $250.00 (medical seminar registration only)
CREDIT: 27 hours
CONTACT: Maxcine Fry (801) 355-7477

November 6

SPONSOR: LDS Hospital
TITLE: **Postgraduate Course—Renal/Pulmonary Syndromes**
LOCATION: Hotel Utah, Salt Lake City
FEE: To be announced
CREDIT: To be announced
CONTACT: C. DuWayne Schmidt, MD (801) 350-1813

November 13-14

SPONSOR: University of Utah
TITLE: **Advanced Trauma Life Support**
LOCATION: Tri-Arc Travelodge, Salt Lake City
FEE: $300.00
CREDIT: 17 hours
CONTACT: Tricia Neilson, RN (801) 533-6435

January 16-20, 1982

SPONSOR: University of Utah
TITLE: **Immune Consequences of Thermal and Traumatic Injury**
LOCATION: Snowbird
FEE: $200-$225
CREDIT: 19 hours
CONTACT: John L. Ninnemann, PhD (801) 581-7617

Note: Dates, times, places and programs are subject to change on occasion. Please check with the sponsoring organization or the Academy for details.

Index to

The Western Journal of Medicine Advertising

AMERICAN MEDICAL ASSOCIATION
Clinical Update Meeting—Hawaii 11
ARTHRITIS FOUNDATION 6
AYERST LABORATORIES
Premarin 20, 21, 22
BANK OF AMERICA
Professional Practice Management 27
BRISTOL LABORATORIES
Tegopen 14, 15
BURROUGHS WELLCOME CO.
Zyloprim 18
CLASSIFIED 34, 36, 38, 39
DOCTORS' CO., THE 33
ELI LILLY AND COMPANY
Ceclor 3
ENDOCRINE-METABOLIC CENTER & PROVIDENCE HOSPITAL OAKLAND
3rd Annual Symposium 30
FBN DATA SYSTEMS 30
HELIOSYSTEMS 13
INSURANCE CORPORATION OF AMERICA 5
MARRIAGE & DIVORCE COUNSELLING WORKSHOP 24
NATIONAL KIDNEY FOUNDATION OF NORTHERN CALIFORNIA
14th Annual Symposium on Renal Disease 24
PRITIKIN RESEARCH FOUNDATION
1981 Symposium on Obesity & the Cardiovascular Diseases .. 38
PUREPAC PHARMACEUTICAL COMPANY 35
RESEARCH INDUSTRIES CORPORATION
RIMSO-50 37
ROCHE LABORATORIES
Bactrim 16, 17, 18
Dalmane ..... 2nd Cover, 1, 2
Limbitrol 28, 29, 30
Valium ..... 3rd and 4th covers
SMITH, KLINE & FRENCH CO.
Dyazide 32
E. R. SQUIBB & SONS INC.
Corgard 9, 9, 10
UNIVERSITY MICROFILMS INTERNATIONAL 40
UNIVERSITY OF PITTSBURGH
8th Annual Symposium—Ear, Nose & Throat Diseases 18
WESTERN JOURNAL OF MEDICINE, THE
Subscription 31
WYETH LABORATORIES
Ativan 24, 25

NORTHEAST
1982